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(54) Title: SULFONAMIDE DERIVATIVES AS CELL ADHESION MODULATORS

(57) Abstract

There are disclosed novel substituted naphthyl-, quinolyl- and isoquinolyl- sulfonamide derivatives that are useful in a method of treating immuno-inflammatory diseases in a mammalian patient suffering therefrom. Pharmaceutical compositions containing the sulfonamide compounds are also provided.

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SULFONAMIDE DERIVATIVES AS CELL ADHESION MODULATORS

FIELD OF THE INVENTION

The present invention describes the discovery of substituted naphthyl-, quinolyl- and isoquinolyl-sulfonamide derivatives which inhibit LFA-1-mediated cell adhesion and aggregation of lymphocytes. The compounds are useful in treating specific and non-specific inflammation, ischemia reperfusion, transplant rejection and asthma. Pharmaceutical compositions containing the sulfonamide compounds are also provided.

BACKGROUND OF THE INVENTION

Each of the publications and patent documents referred to in this document is hereby incorporated by reference in its entirety.

Vascular endothelial cells form the interface between blood and tissues and control the passage of leukocytes as well as plasma fluid into tissues. A variety of signals generated at the site of inflammation can activate both endothelial cells as well as circulating leukocytes so that they become more adhesive to one another. Activation of endothelium and leukocytes initiates a complex adhesion cascade. This adhesion cascade involves the "tethering" of the leukocytes to the endothelium, after which they "roll" along the endothelial surface and finally strongly adhere and migrate into tissue to perform host defense

functions. Several adhesion molecules, belonging to a super gene family consisting of non-covalently associated heterodimeric proteins called integrins, have been identified as being involved in leukocyte-endothelial cell interactions.

The β_2 integrin subfamily includes LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, CR3) and p150/95 (CD11c/CD18, CR4). The known ligands for LFA-1 are ICAM-1, ICAM-2 and ICAM-3. The Intracellular Adhesion Molecules (ICAMs) are also members of the Ig gene superfamily. ICAM-1 is the most ubiquitous of the ICAMs, being expressed at low levels on most peripheral blood leukocytes as well as endothelial cells, fibroblasts and dendritic cells. Cytokine activation of endothelial cells induces a dramatic increase in the expression of ICAM-1 and LFA-1/ICAM-1 interactions which are integral to both lymphocyte adhesion and transmigration of lymphocytes through the endothelial barrier (Dustin, M.L. et al., J. Immunol., 137, 245-254 (1986)). ICAM-2 is primarily constitutively expressed on endothelial cells (de Fougerolles, A.R. et al., J. Exp. Med., 174, 253-267 (1991)); ICAM-3 is largely found on resting lymphocytes, monocytes and neutrophils. Both show increased expression upon T cell activation (de Fougerolles, A.R. and Springer, T.A., J. Exp. Med., 175, 185-190 (1992)).

In addition to its critical role in mediating cellular adhesion, ICAM-1 has also been shown to act as a receptor for a subgroup of rhinoviruses and soluble ICAM-1 has been shown to act as specific inhibitor of rhinovirus infection (Martin, S. D. et al., Nature, 344, 70-72 (1990)). A compound which blocks the interaction of rhinovirus with ICAM-1 may be a powerful pharmacological agent for the prevention and treatment of colds and secondary complications arising from rhinovirus infection.

Support for the importance of β_2 integrins in mediating inflammatory responses has been demonstrated by the ability of monoclonal antibodies which recognize LFA-1 to block CTL-mediated lysis of target cells, as well as inhibiting proliferation of T cells in response to soluble antigens, alloantigens and mitogen. Pathologies relating to a deficiency of β_2 integrin expression include clinical abnormalities including delayed separation of the umbilical stump and patent urachus, poor wound healing and the absence of pus formation, recurrent bacterial and fungal infections, focal or spreading skin and subcutaneous infections, otitis, mucositis, gingivitis, periodontitis, and neutrophilia in the absence of infection (Anderson and Springer, Ann. Rev. Med., 38:175 (1987); Springer et al., J. Exp. Med., 160:1901 (1984)).

Several *in vivo* models have demonstrated the importance of β_2 integrins in delayed-type hypersensitivity. α-LFA-1 antibodies have been shown to block the migration of spleen T cells to sites of dermal inflammation as well as the homing of lymph node and spleen T cells to peripheral and mesenteric lymph node in rats (Issekutz, T. B., J. Immunol., 149, 3394-3402 (1992)). Both α-LFA-1 and α-ICAM-1 antibodies can reduce ear swelling caused by edema and cell infiltration in association with delayed-type hypersensitivity (Scheynius, A. et al., J. Immunol., 150, 655-663 (1993)).

The role of β_2 integrins in allograft rejection has been demonstrated by the ability of α-ICAM-1 antibodies to control allograft rejection and reperfusion injury in humans (Cosimi, A. B. et al., J. Immunol., 144, 4604-4612 (1990); Haug et al., Transplantation, 55, 766-773 (1993)).

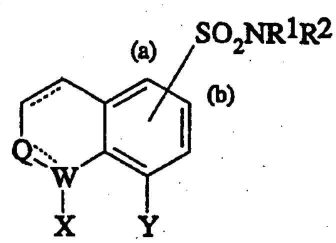
Anti-ICAM-1 antibodies have also been shown to attenuate airway eosinophilia, hyper-responsiveness and asthma symptoms in a primate asthma model.

SUMMARY OF THE INVENTION

A primary objective of the present invention is to provide compounds which are effective in a broad method of treating immuno-inflammatory diseases in a mammalian patient, particularly in a human patient suffering from such a disease.

Another objective of the present invention is to provide a method of preventing or treating immuno-inflammatory diseases in a mammalian patient, particularly in a human, wherein the immuno-inflammatory disease is selected from the group consisting of specific and non-specific inflammation, transplant rejection, allograft rejection, ischemia reperfusion injury, asthma/allergy, delayed type hypersensitivity, contact hypersensitivity, rheumatoid arthritis, rhinovirus and lymphotrohpic virus infections, particularly infections by human immunodeficiency virus (HIV).

In accordance with these objectives, the present invention provides novel compounds which are useful in therapeutic methods of treating immuno-inflammatory diseases in a mammalian patient, especially humans. These novel compounds have the following Formula (I):



(I);

wherein W, Q, (a) and (b), X and Y, and R^1 and R^2 are defined in detail below.

The compound 3-(2-naphthylsulfonyl)-3-azabicyclo[3.2.2]nonane and salts thereof are excluded from the above described novel Formula (I) compounds by proviso; however, this compound is encompassed by and

useful in the advantageous methods of treatment and pharmaceutical compositions that are disclosed below.

In accordance with the objectives of the present invention, there are also provided novel pharmaceutical compositions that are useful in a method of treating an immuno-inflammatory disease in a patient suffering from such a disease. The pharmaceutical compositions provided contain a pharmaceutically effective amount of one or more of the Formula (I) compounds of the present invention in combination with a pharmaceutically acceptable carrier or diluent therefor, for treating an immuno-inflammatory disease in a mammalian patient suffering therefrom.

In accordance with the objectives of the present invention, there is also provided an advantageous method of treating immuno-inflammatory diseases in a patient suffering therefrom. The method entails administering a pharmaceutically effective amount of a Formula (I) compound to the patient, preferably in the form of a pharmaceutical composition as provided for herein. Exemplary of such diseases are specific and non-specific inflammation, transplant rejection, allograft rejection, ischemia reperfusion injury, asthma/allergy, delayed type hypersensitivity, contact hypersensitivity, rheumatoid arthritis, rhinovirus, and lymphotrophic viruses, including human immunodeficiency virus (HIV).

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided as an aid to those desiring to practice the present invention. The present invention, however, is not limited by this description or the Examples provided herein; the scope of the invention is defined by the claims following. One of ordinary skill in the art will readily realize that various changes can be made in the materials and procedures set forth herein without

departing from the spirit or scope of the present inventive discovery.

To better facilitate a thorough understanding of the present inventive discovery, the Detailed Description of the Invention is divided into the following parts:

Part I	-	Glossary of Terms and Abbreviations
Part II	-	Description of Compounds of the Invention
Part III	-	Syntheses and Examples
Part IV	-	Pharmacology and Biological Assays
Part V	-	Table of Selected Compounds
Part VI	-	Pharmaceutical Compositions

Part I - Glossary of Terms and Abbreviations

In order to remove any ambiguity which may exist with respect to the meanings of certain terms and abbreviations which are used herein, the following glossary is provided. Generally, the definitions provided below are well-known in the art, and are consistent with art-recognized usages.

BCECF:	2′,7′-bis-(2-carboxyethyl)-5- (and 6-) carboxyfluorescein
BCECF-AM:	2′,7′-bis-(2-carboxyethyl)-5- (and 6-) carboxyfluorescein acetoxymethyl ester (Molecular Probes Cat. No. B-1170)
Boc:	Butyloxycarbonyl
BOP:	Benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl:	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Cbz:	Benzyloxycarbonyl
DIEA:	Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
DME:	Dulbecco′s Modified Eagle′s Medium

DMEM-HSA: Dulbecco's Modified Eagle's Medium with 2.5 mg/ml Human Serum Albumin
DMF: Dimethylformamide
ECs: Endothelial cells
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EGM-UV: Endothelial Cell Growth Medium - Umbilical Vein (Clonetics, Corp.)
EtOAc: Ethyl Acetate
EtOH: Ethanol
Et_2O: Diethyl ether
furan(2): 2-Furyl
furan(3): 3-Furyl
HBSS: Hank's Balanced Salts Solution
HSA: Human Serum Albumin
IC_{50}: Inhibitory concentration, concentration at which adhesion is inhibited to 50% of control level.
MeOH: Methanol
NMR: Nuclear Magnetic Resonance
PBS: Phosphate Buffered Saline
Ph: Phenyl
PPh_3: Triphenylphosphine
Py(2): 2-Pyridyl
Py(3): 3-Pyridyl
Py(4): 4-Pyridyl
PPh_3O: Triphenylphosphine oxide
TFA: Trifluoroacetic acid
TFAA: Trifluoroacetic anhydride
TNF-α: Tumor Necrosis Factor-Alpha

In this application, a "Chromatotron" is a device for rapid, preparative silica gel thick layer chromatography. The method relies upon centrifugal force to speed the movement of the solvent front across a circular thick layer chromatographic plate radially from the center. Unless otherwise noted, the matrix of

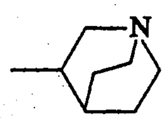
the thick layer plate is silica gel. A suitable device is the Chromatotron Model 8924, commercially available from Harrison Research, USA.

"Flash chromatography" is a method of rapid purification by low pressure silica gel chromatography in a column format.

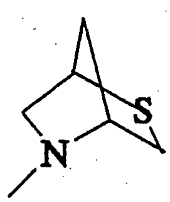
"Radial chromatography," refers to the Chromatotron.

To avoid possible ambiguity as to nomenclature, the structural definitions of the typical formulae of R^1, R^2 or NR^1R^2 are provided below. In these illustrations, when the free bond comes off of a nitrogen atom, then NR^1R^2 is shown. On the other hand, when the free bond comes off of a carbon atom, then R^1 or R^2 is shown.

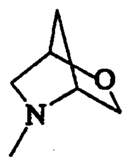
3-quinuclidinyl:



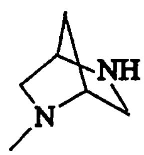
2-thia-5-azabicyclo[2.2.1]hept-5-yl:



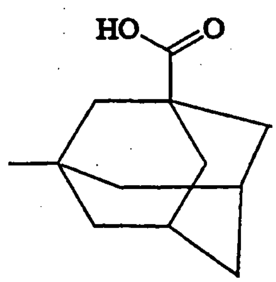
2-oxa-5-azabicyclo[2.2.1]hept-5-yl:



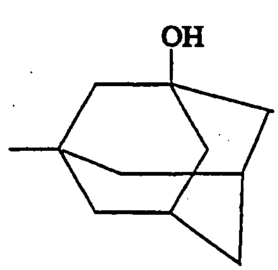
2,5-diazabicyclo[2.2.1]hept-2-yl:



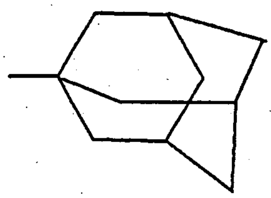
3-carboxy-1-adamantyl or 3-carboxytricyclo[$3.3.1.1^{3,7}$]dec-1-yl:



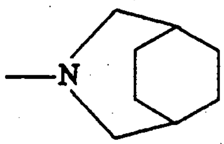
3-hydroxy-1-adamantyl or 3-hydroxytricyclo[$3.3.1.1^{3,7}$]dec-1-yl:



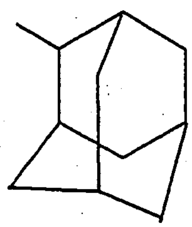
1-adamantyl or tricyclo[3.3.1.1^{3,7}]dec-1-yl:



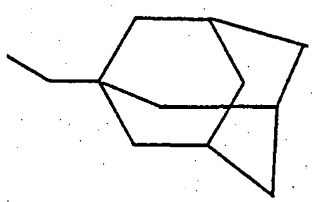
3-azabicyclo[3.2.2]non-3-yl:



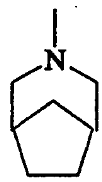
2-adamantyl or tricyclo[3.3.1.1.^{3,7}]dec-2-yl:



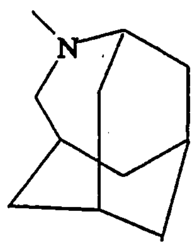
1-adamantanemethyl or 1-adamantylmethyl:



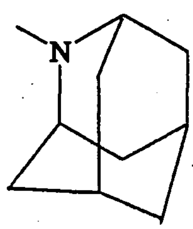
3-azabicyclo[3.2.1]oct-3-yl:



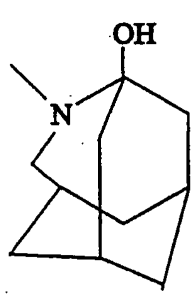
4-azahomoadamant-4-yl or 2-azatricyclo[4.3.1.$1^{4,8}$]undec-2-yl:



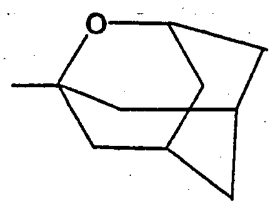
2-azaadamant-2-yl or 2-azatricyclo[3.3.1.$1^{3,7}$]dec-2-yl:



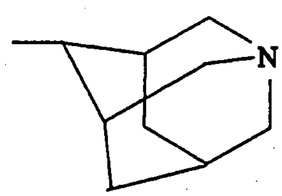
3-hydroxy-4-azahomoadamant-4-yl or 1-hydroxy-2-azatricyclo[4.3.1.$1^{4,8}$]undec-2-yl:



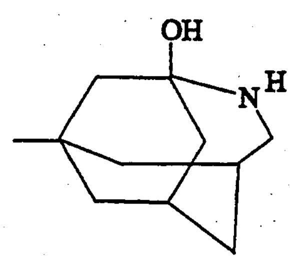
2-oxaadamant-1-yl or 2-oxatricyclo[3.3.1.1^{3,7}]dec-1-yl:



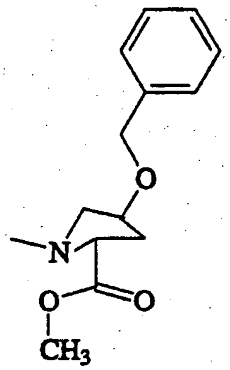
1-azaadamant-4-yl or 1-azatricyclo[3.3.1.1^{3,7}]dec-4-yl:



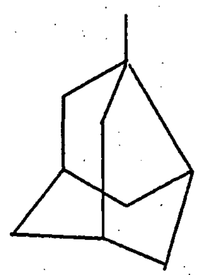
1-hydroxy-2-azahomoadamant-8-yl or 1-hydroxy-2-azatricyclo[4.3.1.1^{4,8}]undec-8-yl:



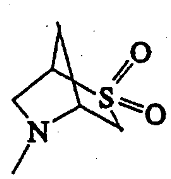
4-benzyloxy-2-methoxycarbonylpyrrolidin-1-yl:



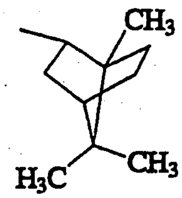
3-noradamantyl or tricyclo[3.2.1.$1^{3,7}$]non-1-yl:



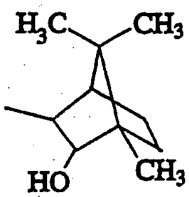
2-thiadioxo-5-azabicyclo[2.2.1]hept-5-yl or 5-aza-2-thiabicyclo[2.2.1]hept-5-yl-2,2-dioxide:



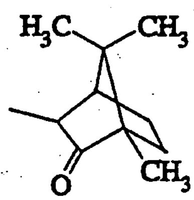
2-bornyl or 1,7,7-trimethyl bicyclo[2.2.1]hept-2-yl:



2-hydroxy-1,7,7-trimethyl bicyclo[2.2.1]hept-3-yl:

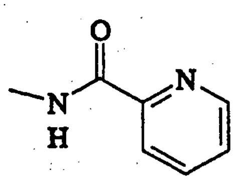


2-oxa-1,7,7-trimethyl bicyclo[2.2.1]hept-3-yl:

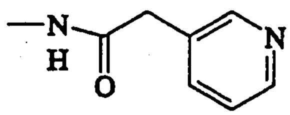


Also, the following structures are presented to illustrate the nomenclature used for residues of X and Y in the Table 1:

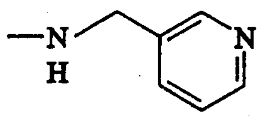
NHCO-Py(2):



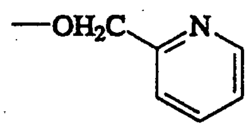
$NHCOCH_2$-Py(3):



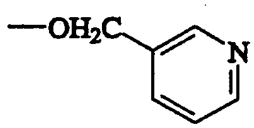
$NHCH_2$-Py(3):



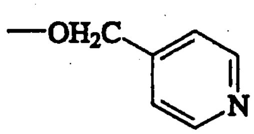
OCH_2-Py(2):



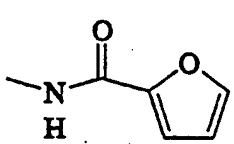
OCH_2-Py(3):



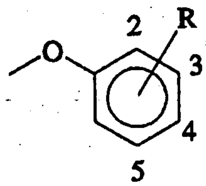
OCH_2-Py(4):



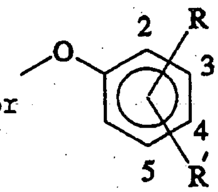
NHCO-Furan(2):



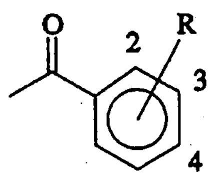
OPh-R or OPh-R,R':



or

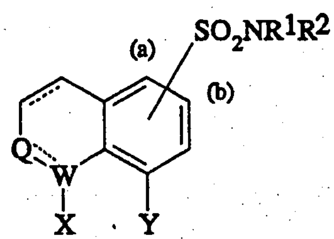


-COPh-R:



Part II - Description of Compounds of the Invention

The compounds of the present invention are those of the Formula (I):



(I)

wherein:

W and Q are selected from a carbon and a nitrogen atom, provided that W and Q are not both simultaneously nitrogen atoms;

wherein (a) and (b) denote the ring positions which can be substituted with the sulfonamide group;

wherein dashed bonds indicate optionally saturated or unsaturated bonds;

wherein X and Y can be the same or different and are selected from a hydrogen atom, a halogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, -CN, $-NO_2$, $-SO_2NH_2$, $-COOR^3$, $-(CH_2)_mOR^3$, $-CONHR^4$, $-NHCO(CH_2)_nR^5$, $-NH(CS)NH(CO)_pR^6$, $-NH(CO)NHR^7$, or $-(CO)_qNR^8R^9$, wherein m is an integer of 0 to 3, n is an integer of 0 to 3, p is 0 or 1 and q is 0 or 1;

wherein R^1 and R^2 are the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, amine-substituted C_{1-8} alkyl, C_{3-9} cycloalkyl, aryl, 1-adamantyl, 2-adamantyl, 1-adamantanemethyl, 3-noradamantyl, 3-quinuclidinyl, 3-carboxy-1-adamantyl, 2-oxaadmant-1-yl, 1-azaadamant-4-yl, 3-hydroxy-1-adamantyl, 1-hydroxy-2-azahomoadamant-6-yl, 1-hydroxy-4-azahomoadamant-4-yl, 2-oxa-1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, and 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl.

Alternatively, R^1 and R^2 together with the nitrogen atom to which they are attached form either (i) a substituted or unsubstituted monocyclic moiety containing from 5 to 15 ring atoms, or (ii) a substituted or unsubstituted bridged polycyclic moiety containing from 7-20 ring atoms. The monocyclic moieties (i) are preferably those which contain 5 to 10 ring atoms, most preferably 5 or 6 ring atoms. The polycyclic moieties (ii) are preferably those containing 7 to 16 ring atoms, most preferably 7 to 9 ring atoms, and are bicyclic or tricyclic. When substituted, the substituents that can be appended to the monocyclic or polycyclic moieties are preferably C_{1-3} alkyl, hydroxy, amino, C_{1-3} alkyl-mono- or di-substituted amino, carboxy-C_{1-3} alkyl esters or a keto- group. One to four substituents can be appended to the rings and, when present, preferably one or two substituents are appended.

Except for the nitrogen atom in the $-NR^1R^2$ moiety, the ring atoms of the monocycles (i) and polycycles (ii) are usually all carbon atoms but can also include additional heteroatoms. One, two or three additional heteroatoms can be present. The additional heteroatoms are preferably sulfur, but can also be nitrogen and/or oxygen. Sulfur ring heteroatoms can also be present as sulfones. It is most preferred that there be no heteroatom in the rings of the monocycles (i) or polycycles (ii) other than the nitrogen of the $-NR^1R^2$ moiety.

R^3 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, carboxy-substituted C_{1-8} alkyl, C_{1-8} alkyl substituted by a substituted or unsubstituted aliphatic heterocyclic group, aryl, heteroaryl, substituted aryl, substituted heteroaryl, substituted or unsubstituted aryl-substituted C_{1-8} alkyl, substituted or unsubstituted heteroaryl-substituted C_{1-8} alkyl, C_{2-8} alkanoyl, amine-substituted C_{1-8} alkyl and $-(CH_2)_r(CO)_sR^{10}$, wherein R^{10} is a hydrogen atom, -OH, C_{1-8} alkyl, C_{1-8} alkyloxy, amine-substituted C_{1-8} alkyl or a substituted or unsubstituted 5- or 6-membered saturated or unsaturated heterocyclic group containing at least one nitrogen atom; r is an integer ranging from 1 to 3 and s is 0 or 1.

R^4 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{11}$, wherein R^{11} is hydrogen or C_{1-8} alkyl, and $-NR^{12}R^{13}$, wherein R^{12} and R^{13} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl.

R^5 is selected from the group consisting of a hydrogen atom, a halogen atom C_{1-8} alkyl, C_{1-8} alkyloxycarbonylamino, $-NH_2$, di-C_{1-8} alkylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxy, aryl-substituted C_{1-8} alkyloxy, heteroaryl-substituted C_{1-8} alkyloxy, amine-substituted C_{1-8} alkyl, and a substituted or unsubstituted 5- or 6-membered saturated or unsaturated heterocyclic group containing at least one nitrogen atom and optionally, one oxygen atom or one sulfur atom.

R^6 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{14}$, wherein R^{14} is hydrogen atom or C_{1-8} alkyl, and $-NR^{15}R^{16}$, wherein R^{15} and R^{16} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl.

R^7 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{17}$, wherein R^{17} is hydrogen or C_{1-8} alkyl, and $-NR^{18}R^{19}$, wherein R^{18} and R^{19} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl.

R^8 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl,

heteroaryl-substituted C_{1-8} alkyl, C_{1-8} alkyloxycarbonyl and a benzyloxycarbonyl group; wherein said aryl, heteroaryl or benzyloxycarbonyl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{20}$, wherein R^{20} is a hydrogen atom or C_{1-8} alkyl.

R^9 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl, C_{1-8} alkyloxycarbonyl and a benzyloxycarbonyl group; wherein said aryl, heteroaryl or benzyloxycarbonyl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, a C_{1-4} carboxylic acid and $-CO_2R^{21}$, wherein R^{21} is hydrogen or C_{1-8} alkyl, or $-NR^8R^9$ can form a saturated heterocyclic group containing 5 or 6 ring atoms.

Pharmaceutically acceptable salts of the compounds of the formula I are included within the present invention. Such salts are preferably hydrogen halide, sulfate or bisulfate, phosphate or hydrogen phosphate salts of the various amines in the compound. Of the hydrogen halide salts, chloride and bromide salts are preferred. Also, alkali metal and alkaline earth metal salts of any acid groups present in the compounds according to formula I are contemplated.

The compound 3-(2-naphthylsulfonyl)-3-azabicyclo[3.2.2]nonane and its salts are excluded from Formula (I).

In the above Formula I, aryl groups are preferably selected from the group consisting of phenyl, biphenyl, and naphthyl. A heteroaryl group is preferably a mono- or bicyclic aromatic system containing one, two, three or four heteroatoms selected from nitrogen, oxygen and sulfur atoms. Examples of preferred heteroaryl groups

are pyridyl, pyrazinyl, thiazolyl, isoxazolyl, pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, imidazolyl, benzimidazolyl, and indolyl.

Also, when any heteroaryl group is a pyridyl derivative, the corresponding N-oxide is also included within the scope of the compounds of the invention.

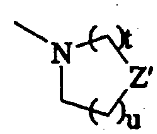
In Formula I, "C_{1-8} alkyl" throughout can be straight or branched chains. C_{1-8} alkyl groups are preferably C_{1-6} alkyl groups, and most preferably are C_1, C_2 or C_3 groups. Similarly, C_{2-8} alkenyl and C_{2-8} alkanoyl groups are preferably C_{2-4} alkenyl and C_{2-4} alkanoyl groups, respectively.

In Formula I, halogen substituents are preferably F, Cl or Br, most preferably Cl.

In Formula I, referring to R^3, R^5 and R^{10}, substituted or unsubstituted 5- or 6- membered, saturated or unsaturated, heterocyclic groups containing at least one nitrogen atom, can contain two nitrogen atoms, but preferably contain only one nitrogen atom. However, the saturated or unsaturated heterocycle can also contain one oxygen atom or one sulfur atom, preferably a sulfur atom. The saturated or unsaturated heterocyclic group is attached either by a nitrogen atom or by a carbon atom in said heterocyclic group.

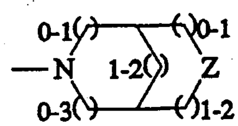
Heterocyclic groups of R^3 are not limited to 5- or 6- member rings containing at least one nitrogen atom.

Preferred compounds of the invention are those wherein, in Formula (I), when R^1 and R^2 together with the nitrogen atom to which they are both attached form a monocyclic moiety, it is preferably a substituted or unsubstituted monocyclic moiety of the following formula:



wherein Z′ is selected from the group consisting of N, S, O, $-CH_2-$, and $-CHR^{22}-$, t and u are each an integer of 0-5, provided that t+u is >0 and R^{22} is selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, aryl, arylalkoxy, heteroaryl, aryl substituted C_{1-8} alkyl, heteroaryl substituted C_{1-8} alkyl, haloaryl substituted C_{1-8} alkyl, 1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2,2,1]hept-3-yl, and 2-hydroxy-1,7,7-trimethyl-bicyclo[2,2,1]hept-3-yl.

In other preferred embodiments of Formula (I), when R^1 and R^2, together with the nitrogen atom to which they are both attached, form a polycyclic moiety, it is preferably a substituted or unsubstituted bicyclic moiety of the following formula



wherein Z is selected from the group consisting of $-CH_2-$, -O-, -S-, $-SO_2-$, $-N(R^{23})-$ and $-NC(O)R^{23}$, wherein R^{23} is selected from a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, aryl, heteroaryl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl, haloaryl-substituted C_{1-8} alkyl, or 1-adamantyl.

Additional preferred embodiments are those wherein R^1 and R^2, together with the nitrogen atom to which they are both attached, form a substituted or unsubstituted bridged bicyclic moiety having 7-12 ring atoms, such as a substituted or unsubstituted bridged bicyclic moiety selected from the group consisting of 3-azabicyclo[3.3.2]dec-3-yl, 3-azabicyclo[3.2.2]non-3-yl, 3-azabicyclo[3.2.1]oct-3-yl, 4-azahomoadamant-4-yl, 2-azaadamant-2-yl, 2-thia-5-azabicyclo[2.2.1]hept-5-yl, 2-oxo-5-azabicyclo[2.2.1]hept-5-yl, 2, 5-

diazabicyclo[2.2.1]hept-2-yl and 1-hydroxy-4-azahomoadamant-4-yl.

Some preferred compounds of the Formula (I) of the present invention are the following:

(a) a compound of the Formula (I), wherein in R^3, the substitutions of said substituted aryl group, substituted aliphatic heterocylic group or substituted heteroaryl group number from 1 to 3 and are selected from a C_{1-3} alkyl group, a C_{1-3} alkyloxy group, a halogen-substituted C_{1-3} alkyl group, a C_{1-4} alkloxycarbonyl group, $-NO_2$, -OH and $-NH_2$;

(b) a compound of the Formula (I), wherein in all of R^3 through R^{15}, said aryl groups are phenyl or fluorenyl, and said heteroaryl groups are selected from the group consisting of furyl, pyridyl, pyrazinyl, and 1,3-thiazolyl, and said aliphatic heterocyclic groups are selected from the group consisting of piperidyl, morpholinyl, piperazinyl and pyrrolidinyl;

(c) a compound of the Formula (I), wherein R^1 and R^2, together with the nitrogen atom to which they are both attached, form a moiety selected from the group consisting of piperidyl, 3-azabicyclo[3.3.2]dec-3-yl, 3-azabicyclo[3.2.2]non-3-yl, 3-azabicyclo[3.2.1]oct-3-yl, 4-azahomoadamant-4-yl, 2-azaadamant-2-yl, 2-thia-5-azabicyclo[2.2.1]hept-5-yl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 5-C_{1-8} alkyloxycarbonyl-2,5-diazabicyclo[2.2.1]hept-2-yl, 5-benzyloxycarbonyl-2,5-diazabicyclo[2.2.1]hept-2-yl and 3-hydroxy-4-azahomoadamant-4-yl;

(d) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is a chlorine atom, Y is a hydrogen atom, R^1 is an adamantyl group and R^2 is a hydrogen atom;

(e) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is a chlorine atom, Y is a

hydrogen atom, and R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl, 2-thia-5-azabicyclo[2.2.1]hept-5-yl or 3-azabicyclo[3.2.2]non-3-yl;

(f) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is $-NH_2$, Y is a hydrogen atom and R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl;

(g) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is $-NHCOR^4$ and Y is a hydrogen atom; wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl; and R^4 is a heteroaryl group;

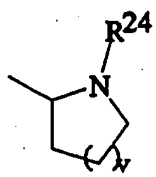
(h) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is $-NHCOR^4$ and Y is a hydrogen atom; wherein R^1 and R^2, together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl, and R^4 is a substituted pyridyl, substituted pyridyl N-oxide or a substituted pyrazinyl

(i) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is a hydrogen atom and Y is $-OR^3$; wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form either 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl; and R^3 is mono-, di- or tri-substituted phenyl, wherein at least one substituent of said phenyl group is $-NO_2$;

(j) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is a hydrogen atom and Y is OR^3; wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl and R^3 is pyridyl methyl or pyridyl N-oxide methyl;

(k) a compound of the Formula (I), wherein Q and W are each carbon atoms, X is a hydrogen atom, Y is OR^3, wherein R^1 and R^2 together with the nitrogen atom

to which they are both attached form 4-azahomoadamant-4-yl, R^3 is $-(CH_2)_r(CO)_sR^{10}$, r = 1, 2 or 3, s = 0, R^{10} is an aminoalkyl group having the structure,



wherein v = 1 or 2;

and R^{24} is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyoyloxycarbonyl;

(l) a compound of the Formula (I), wherein in R^4 the amine of said amine-substituted C_{1-8} alkyl is $-NR^{25}R^{26}$, wherein R^{25} and R^{26} can be the same or different and are selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and aryl-substituted C_{1-8} alkyloxycarbonyl;

(m) a compound of the Formula (I), wherein in R^1 or R^2, the amine of said amine-substituted C_{1-8} alkyl is $-NR^{27}R^{28}$, wherein R^{27} and R^{28} can be the same or different and are selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and arylalkyloxycarbonyl;

(n) a compound of the Formula (I), wherein X or Y is $-NH(CO)(CH_2)_nR^5$ and R^5 is a substituted or unsubstituted 5- or 6- membered saturated heterocyclic group containing at least one ring nitrogen atom, and optionally, one ring oxygen atom or one ring sulfur atom, and wherein said saturated heterocyclic group is attached either by said ring nitrogen atom or by a carbon atom;

(o) a compound of the Formula (I), wherein R^5 is a substituted, saturated heterocyclic group containing 5 or 6 ring atoms and at least one ring nitrogen, wherein said substitution is at a ring nitrogen and is selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and arylalkyloxycarbonyl;

(p) a compound of the Formula (I), wherein X or Y is $-NHCO(CH_2)_nR^5$, and R^5 is a saturated heterocyclic group containing a first heteroatom that is nitrogen and a second heteroatom that is nitrogen, oxygen or sulfur;

(q) a compound of the Formula (I), wherein X or Y is $-(CH_2)_mOR^3$ and R^3 is $-(CH_2)_r(CO)_sR^{10}$, wherein R^{10} is a heterocyclic group containing 5 or 6 ring atoms and containing a first ring heteroatom that is nitrogen and a second ring heteroatom that is nitrogen, oxygen or sulfur;

(r) a compound of the Formula (I), wherein NR^1R^2 together form a substituted or unsubstituted bridged polycyclic moiety having 7 to 20 ring atoms, wherein there are no ring heteroatoms in addition to the nitrogen of NR^1R^2;

(s) a compound of the Formula (I), wherein NR^1R^2 together form a substituted or unsubstituted bridged polycyclic moiety having 7 to 20 ring atoms, wherein there is a second ring heteroatom in addition to the nitrogen of NR^1R^2, wherein said second ring heteroatom is nitrogen, oxygen or sulfur;

(t) a compound of the Formula (I), wherein one of X or Y is a hydrogen atom;

(u) a compound of the Formula (I), wherein one of R^1 or R^2 is hydrogen;

(v) a compound of the Formula (I), wherein R^1 and R^2 together form a substituted monocylic moiety

containing from 5-15 ring atoms or a substituted polycyclic moiety containing from 7 to 20 ring atoms; wherein one, two or three of said substitutions are present and are independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2Ph$, -OH, $-CO_2R^{29}$ and $-CONHR^{29}$, wherein R^{29} is a hydrogen atom or C_{1-8} alkyl;

(w) a compound of the Formula (I), wherein in X and/or Y is $-(CO)_qNR^8R^9$, and R^8 and R^9, together with the nitrogen to which they are both attached, form a substituted or unsubstituted saturated heterocyclic group having 5- or 6 ring atoms;

(x) a compound of paragraph (w), wherein the saturated heterocyclic group contains a second heteroatom that is either sulfur or oxygen;

(y) a compound of the Formula (I), wherein the sulfonamide group is attached to the ring at position (b);

(z) a compound of the Formula (I), wherein R^{10} is an amine-substituted C_{1-8} alkyl and said amine is $-NR^{30}R^{31}$, wherein R^{30} and R^{31} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, alkyloxycarbonyl and aryloxycarbonyl;

(aa) a compound of the Formula (I), wherein W and Q are selected from a carbon and a nitrogen atom, provided that W and Q are not both simultaneously nitrogen atoms;

wherein (a) and (b) denote the attachment point of the sulfonamide group;

wherein dashed bonds indicate optionally saturated or unsaturated bonds;

wherein X and Y can be the same or different and are selected from a hydrogen atom, a halogen atom, and a polar heteroaryl group;

wherein R^1 and R^2 are the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, amine-substituted C_{1-8} alkyl, C_{3-9}

cycloalkyl, aryl, 1-adamantyl, 2-adamantyl, 1-adamantanemethyl, 3-noradamantyl, 3-quinuclidinyl, 3-carboxy-1-adamantyl, 2-oxaadmant-1-yl, 1-azaadamant-4-yl, 3-hydroxy-1-adamantyl, 1-hydroxy-2-azahomoadamant-6-yl, 1-hydroxy-4-azahomoadamant-4-yl, 2-oxa-1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, and 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form either (i) a substituted or unsubstituted monocyclic moiety containing from 5 to 15 ring atoms, or (ii) a substituted or unsubstituted bridged polycyclic moiety containing from 7-20 ring atoms.

A "polar heteroaryl group" is expected to increase the water solubility of the compound compared to the same compound lacking the polar heteroaryl group. It is desirable that the compound of the invention have a solubility in distilled water at room temperature of at least 0.04 μg/ml, preferably a solubility of at least 0.4 μg/ml, most preferably a solubility of at least 0.4 mg/ml.

Other preferred compounds are compounds of the Formula (I), wherein Q is a carbon atom, W is a carbon atom or a nitrogen atom, and

X is a hydrogen atom, a halogen atom, hydroxy, $-NH_2$, C_{2-8} alkanoyloxy, $-NHCO(CH_2)_nR^5$, $-NH(CS)NH(CO)_pR^6$ or $-(CO)_qNR^8R^9$;

wherein n = 0 or 3 and R^5 is C_{1-8} alkyl, $-NH_2$, aminophenyl, furyl, pyrazinyl, C_{1-8} alkylpyrazinyl, C_{1-8} alkyl pyridyl or piperidyl;

wherein p = 1 and R^6 is phenyl;

wherein R^8 is a hydrogen atom; and

wherein R^9 is dinitrophenyl-C_{1-8} alkyl;

Y is a hydrogen atom, a halogen atom, hydroxy, C_{1-8} alkyl or $-(CH_2)_mOR^3$;

wherein m = 0 and R^3 is carboxy C_{1-8} alkyl,

C_{1-8} alkyl, pyridyl-C_{1-8} alkyl, C_{1-8} alkyl-pyrrolidinyl-C_{1-8} alkyl or phenyl, wherein said phenyl group is optionally substituted by one or two substituents selected from the group consisting of C_{1-8} alkyl, $-NO_2$, $-NH_2$, and $-CF_3$; and

$-NR^1R^2$ is 1-adamantylamino, (2-oxa-1,7,7-trimethyl-bicyclo[2.2.1]hept-3-yl)amino, 3-azabicyclo[3.2.2]non-3-yl, 3-azabicyclo[3.2.1]oct-3-yl, 4-azahomoadamant-4-yl or 5-aza-2-thiabicyclo[2.2.1]hept-5-yl.

Other, more preferred compounds are compounds of the Formula (I), wherein Q is a carbon atom, W is a carbon atom, dashed bonds include saturated bonds, and

X is a hydrogen atom, a halogen atom, or $-NHCO(CH_2)_nR^5$, wherein n = 0 and R^5 is methylpyrazinyl;

Y is a hydrogen atom or $-(CH_2)_mOR^3$, m = 0, wherein R^3 is methyl or phenyl substituted with one or two substituents selected from methyl, $-NO_2$, $-CF_3$ or pyridylmethyl; and

$-NR^1R^2$ is 3-azabicyclo[3.2.2]non-3-yl or 4-azahomoadamant-4-yl.

It is most preferred that the compound have activity in the endothelial cell adhesion assay (described in Part III, below) so as to exhibit an IC_{50} of 50 μM or less. Accordingly, compounds 3, 5, 15, 16, 18, 27-29, 32, 38-43, 49, 52, 54, 56, 61, 64, 68-73, 75, 77, 79, 81, 96, and 102-117 in the Examples.

The compound of the Formula (I) may exist in the form of an optical isomer based on an asymmetric carbon atom thereof, and the present invention also includes these optical isomers and a mixture thereof.

Part III - Syntheses and Examples

The compounds of the present invention can be prepared using chemical techniques and reactions which are well known in the art. For example, a coupling reaction of an appropriate amine with an appropriate

substituted or unsubstituted naphthalene-, quinoline- or isoquinoline-sulfonylchloride intermediate can provide a desired compound of Formula (I). In this respect, see the coupling reaction procedures set forth in Example 1 and/or Example 5. Overall, it is noted that starting compounds used to prepare the Formula (I) compounds are commercially available. However, if desired such compounds can also be manufactured using techniques well known in the chemical synthesis arts.

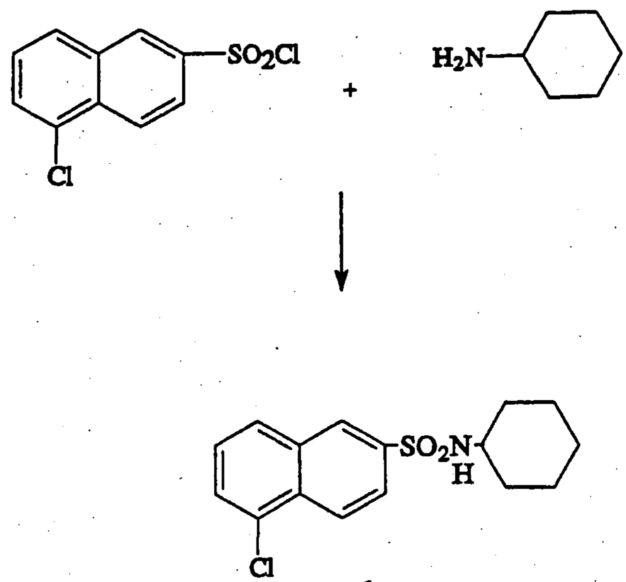
The following synthesis examples are provided as an aid to those desiring to practice the present invention as broadly disclosed herein. Typical syntheses are illustrated below.

SYNTHESIS OF SULFONAMIDES

Various reaction schemes were utilized in the synthesis examples. The various schemes are illustrated below.

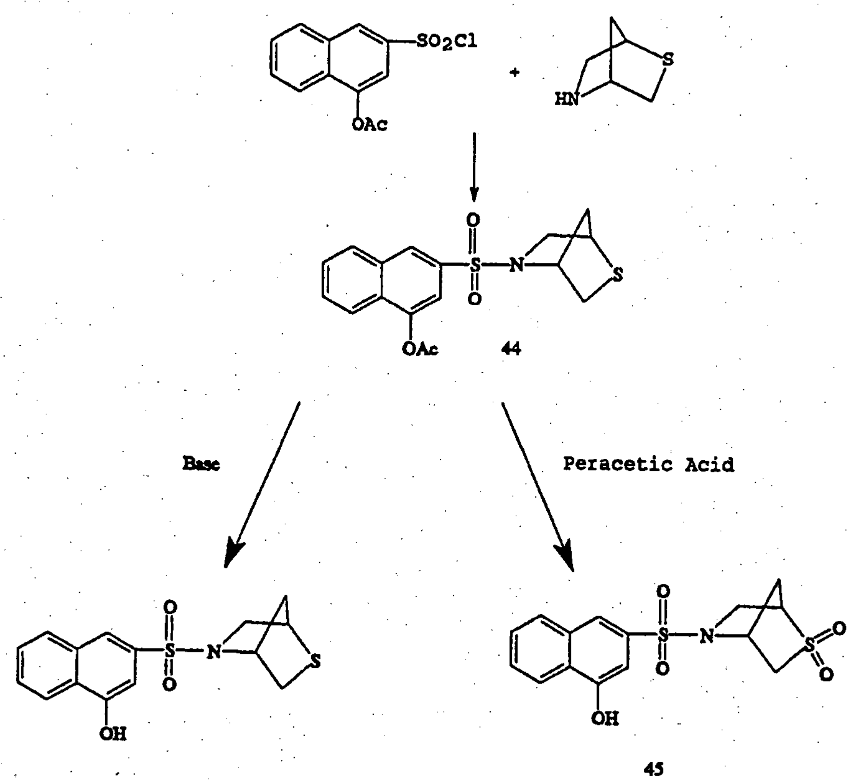
Scheme 1: The compound in Example 1 was prepared using the synthetic Scheme 1 below. The compounds of Examples 1-3, 5, 7-19, 22-31, 35, 38-43, 67 and 121-123 were prepared essentially according to Scheme 1, with

substitution of the appropriate amine.

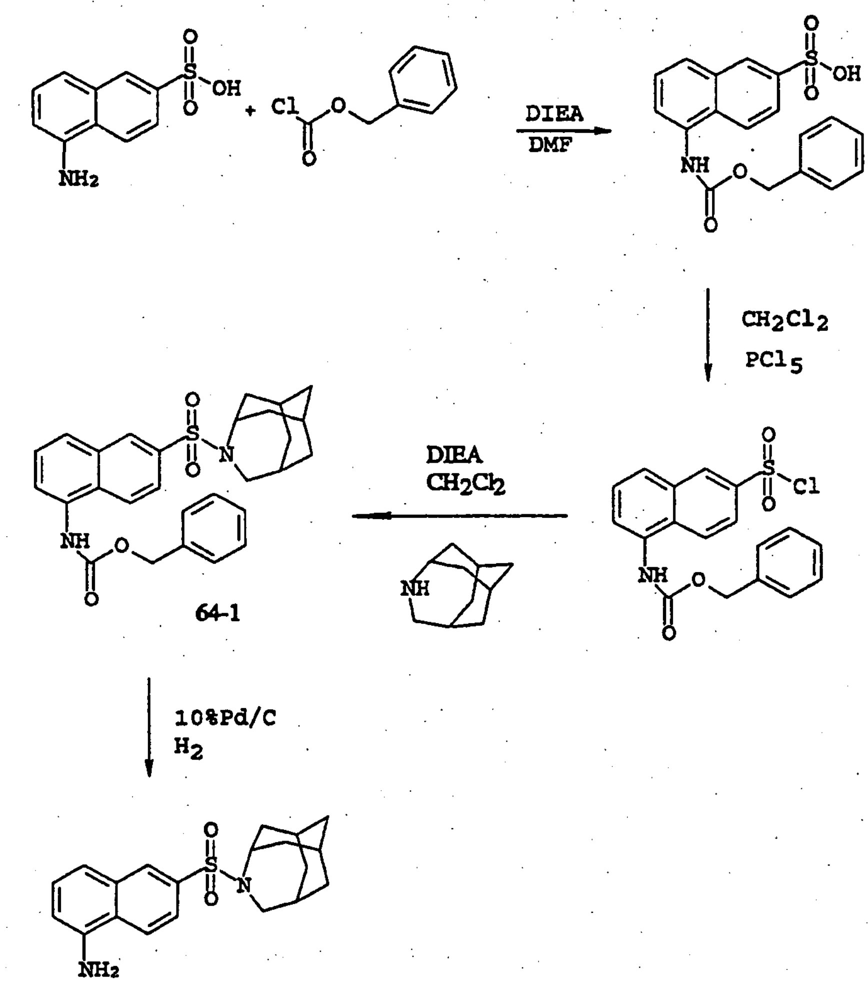


1

Scheme 2: The compounds of Examples 44 and 45 were prepared using the synthetic Scheme 2 below. The compounds of Examples 46-55 were prepared essentially according to Scheme 2, with substitution of the appropriate amine.

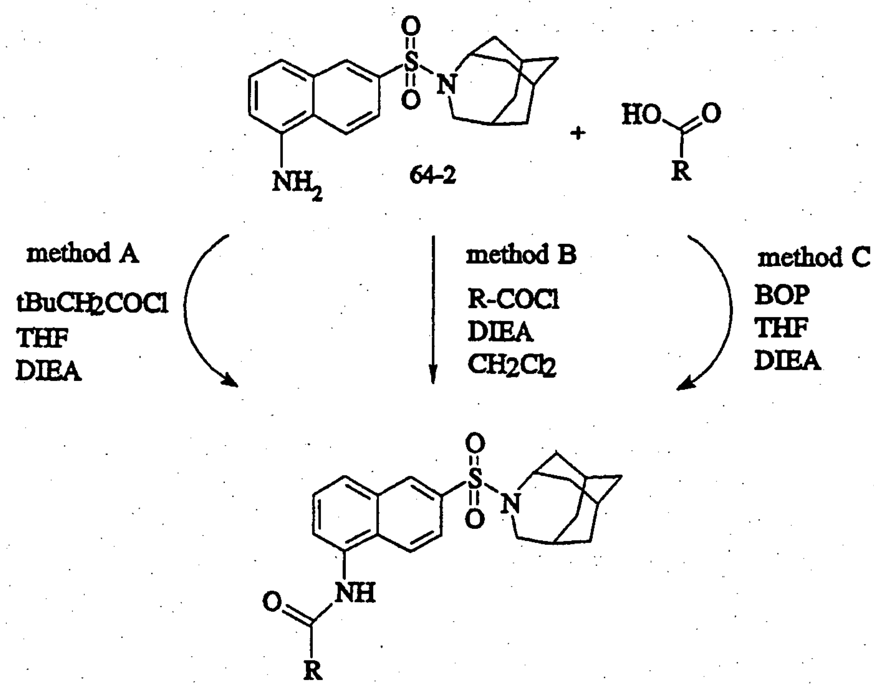


<u>Scheme 3</u> - The compounds 64-1, 64-2, 65-1, 65-2, 66-1 and 66-2 are prepared essentially according to Scheme 3:

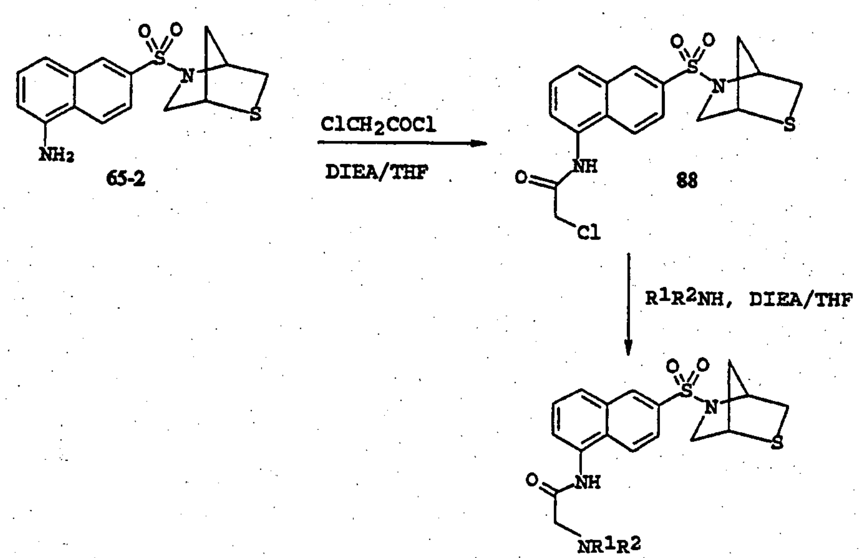


64-2

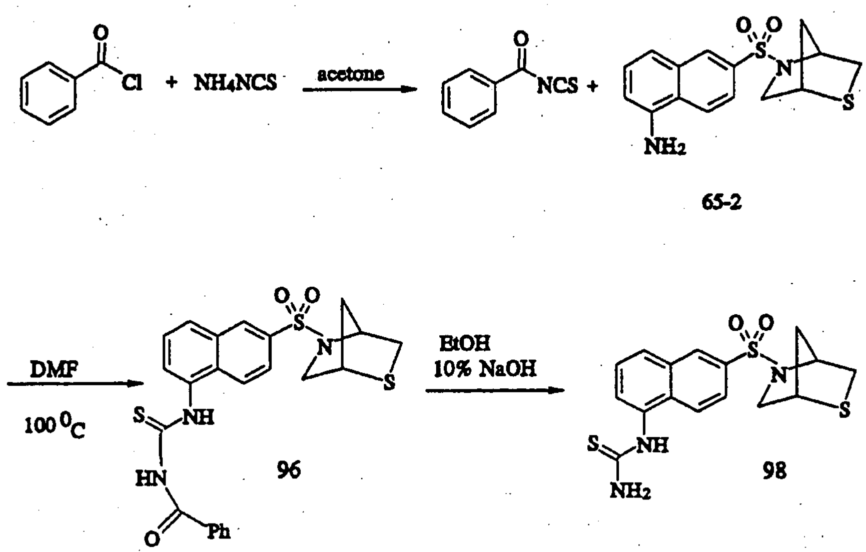
Scheme 4: The compounds in Examples 68-74, 76-78, 80, 82, 84, 86 and 87 are prepared essentially according to Scheme 4:



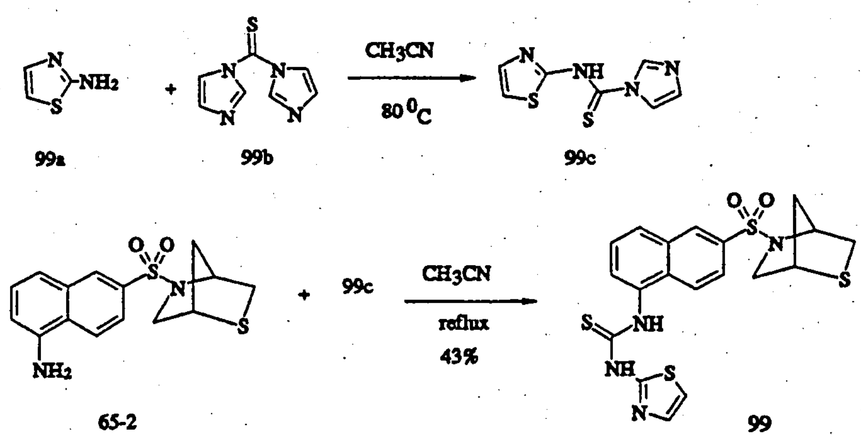
Scheme 5: The compounds in Examples 88-95 are prepared essentially according to Scheme 5:



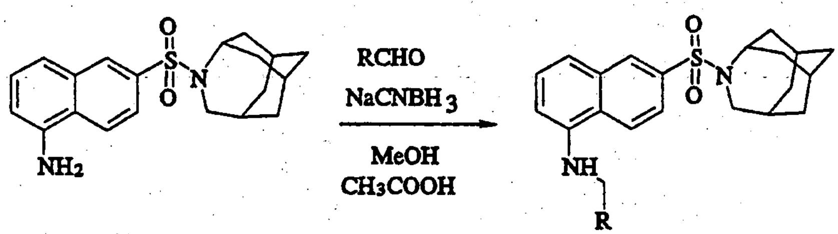
<u>Scheme 6</u>: The compounds in Examples 96-98 are prepared essentially according to Scheme 6:



<u>Scheme 7</u>: The compounds in Examples 99-100 are prepared essentially according to Scheme 7:

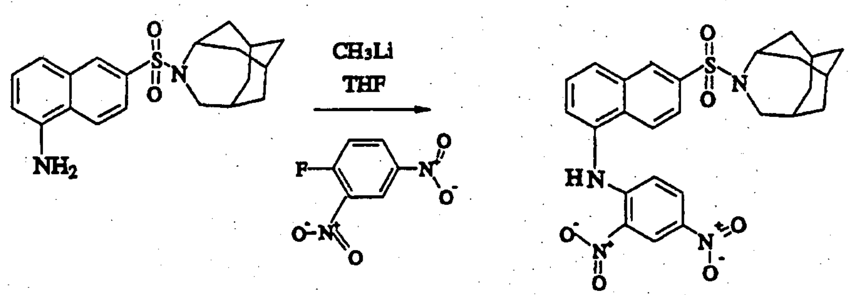


Scheme 8: The compound in Example 101 is prepared according to Scheme 8:

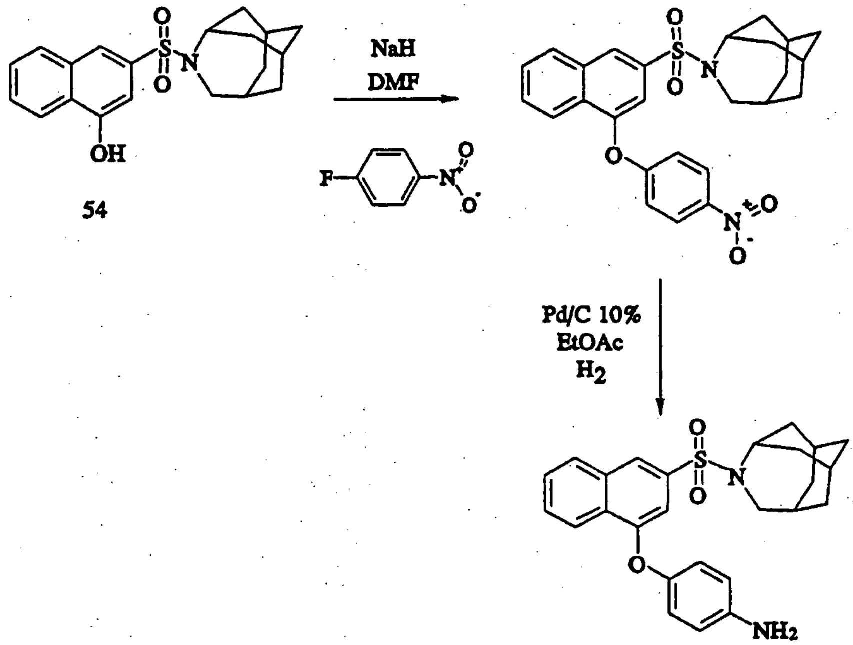


64-2

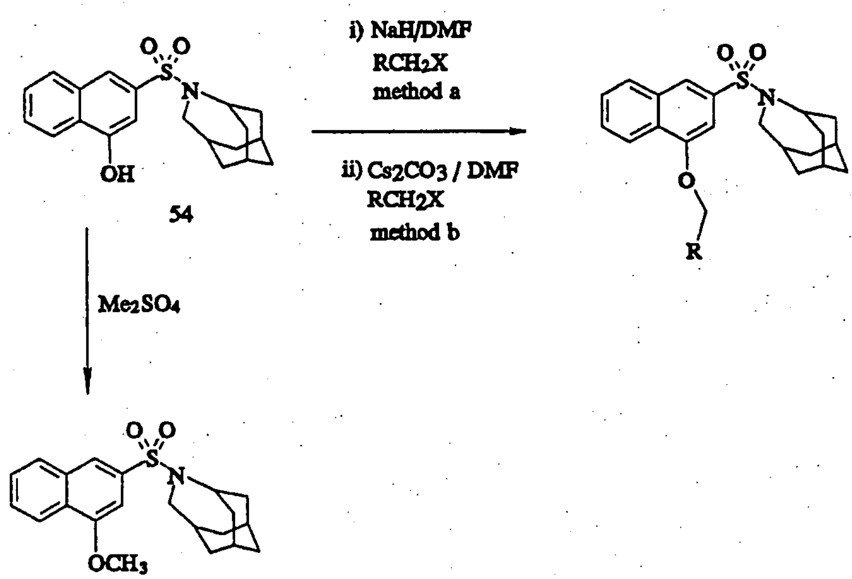
Scheme 9: The compound in Example 102 is prepared according to Scheme 9:



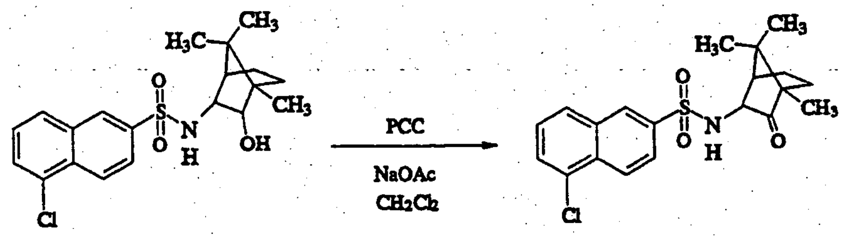
Scheme 10: The compounds in Examples 103-108 are prepared essentially according to Scheme 10:



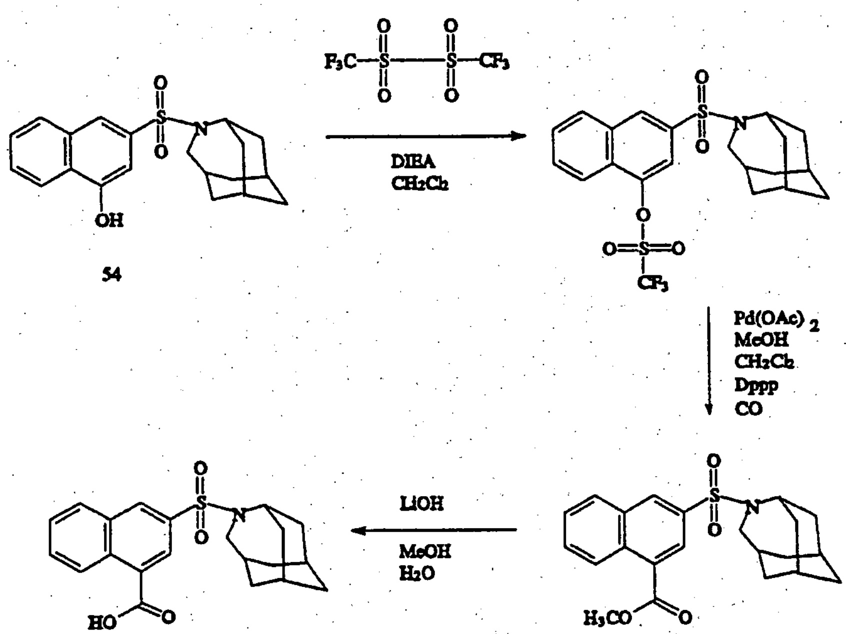
Scheme 11: The compounds in Examples 56-58, 60-63 and 111-116 are prepared essentially according to Scheme 11:



<u>Scheme 12</u>: The compound in Example 117 is prepared according to Scheme 12:

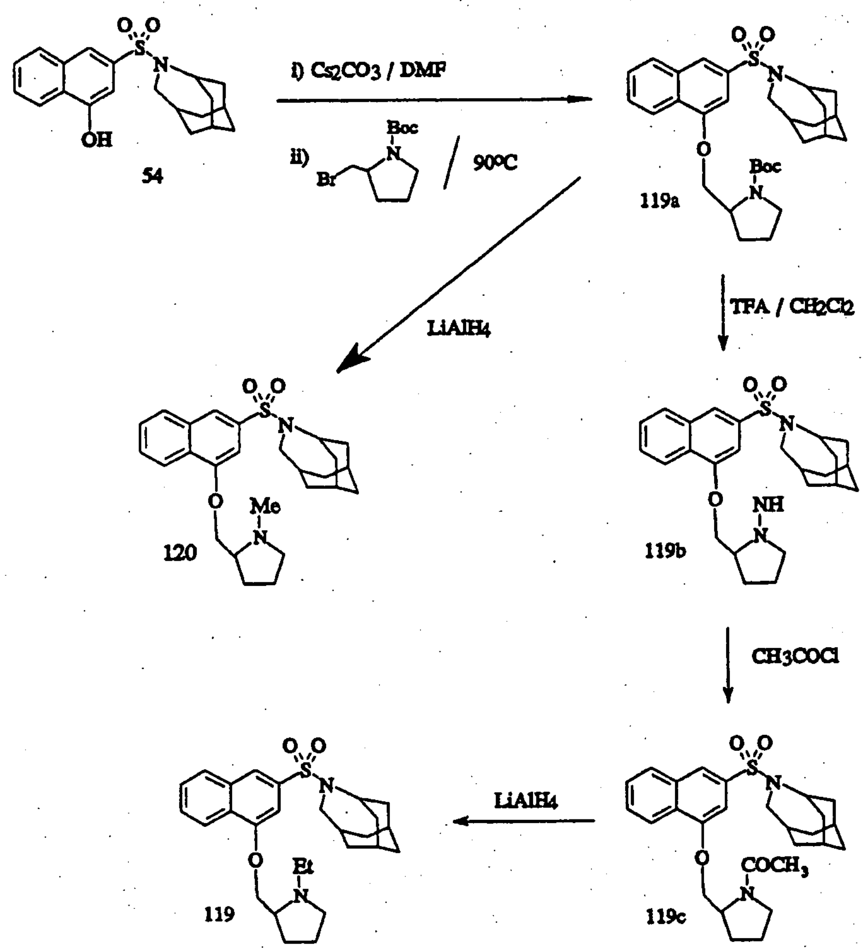


<u>Scheme 13</u>: The compound in Example 118 is prepared according to Scheme 13:

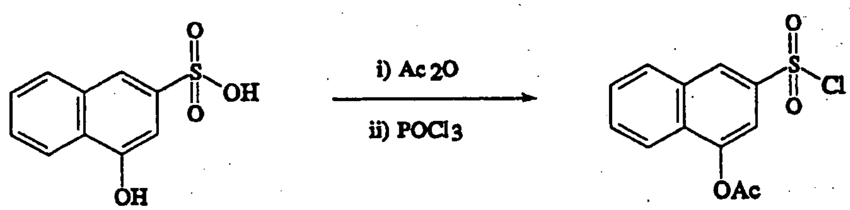


118

<u>Scheme 14</u>: The compounds of Examples 119 and 120 are prepared according to the Scheme 14:



<u>Scheme 15</u>: The intermediate compound in the reference Example 124 is prepared according to Scheme 15:



EXAMPLE 1

5-Chloro-N-cyclohexyl-2-naphthalenesulfonamide

Compound 1 was prepared from the coupling of cyclohexylamine and 5-chloro-2-naphthalenesulfonyl chloride. Cyclohexylamine (1.0 g, 3.8 mmol) and N,N-diisopropylethylamine (DIEA, 1.35 ml, 7.7 mmol) were dissolved in 30 ml chloroform. 5-Chloro-2-naphthalenesulfonyl chloride (0.88 m., 7.7 mmol) in 20 ml chloroform was added dropwise to the solution. After stirring overnight, the chloroform solution was washed with saturated sodium bicarbonate solution and brine. Drying over magnesium sulfate and evaporation of chloroform followed by recrystallization from isopropyl ether/methanol gave 0.92 g (75% yield) of a yellow solid: mp 133-134°C; ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J=1.8, 1 H, H1), 8.38 (d, J=9.0, 1 H, H3), 8.00 (d, J=9.0, 1 H, H4), 7.88 (d, J=8.3, 1 H, H6), 7.71 (d, J=7.5, 1 H, H8), 7.51 (t, J=7.8, 1 H, H7), 5.07 (d, J=7.7, 1 H, NH), 3.23-3.15 (m, 1 H, NCH<u>H</u>, 1.77-1.72 (m, 2 H, ring H's), 1.61-1.55 (m, 2H, ring H's), 1.51-1.45 (m, 1H, ring H), 1.22-1.10 (m, 6H ring H's); anal. calcd. for $C_{16}H_{18}NO_2SCl$; C, 59.34; H, 5.60; N, 4.33; found: C, 59.27; H, 5.60; N, 4.30.

EXAMPLE 2

5-Chloro-N-phenyl-2-naphthalenesulfonamide

Compound 2 was prepared using a procedure similar to the procedure used in Example 1. From 1 g (3.8 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 0.70 ml (7.6 mmol) of aniline, there was obtained a yellow solid. Recrystallization from isopropyl ether/methanol gave brown crystals, 1 g (83% yield): mp 181-183°C; ^{1}H-NMR ($CDCl_3$): δ 8.35 (d, J=1.8, 1 H, H1), 8.31 (d, J=9.0, 1 H, H3), 7.85 (d, J=9.0, 1 H, H4), 7.79 (d, J=8.3, 1 H, H6), 7.69 (d, J=7.5, 1 H, H8), 7.48 (t, J=7.9, 1 H, H7), 7.25-7.19 (m, 2 H, aryl

H's), 7.13-7.06 (m, 3 H, aryl, H's), 6.93 (s, 1 H, NH).

EXAMPLE 3

N-(1-Adamantyl)-5-chloro-2-naphthalenesulfonamide

Compound 3 was prepared using a procedure similar to the procedure used to prepare Compound 1. 1.0 g (3.8 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 1.15 g (7.6 mmol) of 1-adamantanamine afforded the product. Recrystallization from EtOAc gave compound 3 as a yellow solid, 0.81 g (58% yield): mp 202-204°C; ^{1}H NMR ($CDCl_3$): δ 8.47 (d, J=1.8, 1 H, H1), 8.37 (d, J=9.1, 1 H, H3), 7.99 (d, J=9.0, 1 H, H4), 7.88 (d, J=8.2, 1 H, H6), 7.71 (d, J=7.5, 1 H, H8), 7.51 (t, J=7.9, 1 H, H7), 4.82 (s, 1 H, NH), 1.99 (br. s, 3 H, alkyl H's), 1.85-1.80 (m, 6 H, alkyl H's), 1.59-1.50 (m, 6 H, alkyl H's); anal. calcd. for $C_{20}H_{22}NO_2SCl$: C, 63.90; H, 5.90; N, 3.73; found: C, 63.97; H, 5.93; N, 370.

EXAMPLE 4

N-(3-Aminopropyl)-5-chloro-N-phenyl-2-naphthalenesulfonamide

Diethyl azodicarboxylate (1.66 mmol, 0.28 ml) in 3 ml dry THF was added to a mixture of 5-chloro-N-(3-hydroxypropyl)-N-phenyl-2-naphthalenesulfonamide (prepared in a manner similar to compound 1; 1.38 mmol, 0.52 g), phthalimide (0.234 g, 1.66 mmol) and PPh_3 (1.66 mmol, 0.435 g) in 7 ml dry THF, and the mixture was stirred overnight. The solvent was evaporated, and the residue was triturated with Et_2O to give a precipitate which was filtered to give a white powder and yellow filtrate. The white powder (0.44 g) was PPh_3O. The filtrate was evaporated and the residue was suspended in 6 ml EtOH. Hydrazine monohydrate was added which resulted in gas evolution and loss of some color. The solution was brought to reflux and

maintained for 2 hours. A precipitate formed at initial reflux. It was then cooled to room temperature and filtered. The solvent was evaporated to give a yellow oil (0.90 g), which was purified by silica gel chromatography to give 18 mg of a yellow powder, mp: 109-112°C.

EXAMPLE 5

3-(5-Chloro-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 5 was prepared from the coupling of 3-azabicyclo[3.2.2]nonane and 5-chloro-2-naphthalene-sulfonyl chloride. 3-Azabicyclo[3.2.2]nonane (0.31 g, 2.5 mmol) and N,N-diisopropylethylamine (1.0 ml, 5.7 mmol) were dissolved in 10 ml chloroform. 5-Chloro-2-naphthalenesulfonyl chloride (0.50 g. 1.9 mmol) in 20 ml chloroform was added dropwise to the solution. After stirring overnight, the solution was washed with saturated sodium bicarbonate solution and brine.

Drying over magnesium sulfate and evaporation followed by recrystallization from isopropyl ether/methanol gave 0.50 g (76% yield) of compound 5 as a yellow solid: mp 138-139°C; ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J=8.9, 1 H, H3), 8.33 (d, J=1.7, 1 H, H1), 7.91-7.84 (m, 2 H, H4 and H6), 7.72 (d, J=7.5, 1 H, H8), 7.52 (t, J=7.9, 1 H, H7), 3.31 (d, J=4.2, 4 H, N($\underline{CH_2}$R)$_2$), 2.09 (s, 2 H, N(CH$_2\underline{CH}$R)$_2$), 1.75-1.61 (m, 8 H, alkyl H's); anal calcd. for $C_{18}H_{20}NO_2SCl$: C, 61.79; H, 5.76; N, 4.00; found: C, 61.89; H, 5.80; N. 4.08.

EXAMPLE 6

N-(2-Adamantyl-)-N-(3-aminopropyl)-5-chloro-2-naphthalenesulfonamide

5-Chloro-N-(2-adamantyl)-N-(3-hydroxypropyl)-2-naphthalenesulfonamide (prepared in a manner similar to the synthesis of compound 1; 300 mg, 0.69 mmol) was combined with phthalimide (107 mg, 0.73 mmol), and

triphenylphosphine (190 mg, 0.73 mmol) in dry THF (5 ml). This solution was added dropwise to a solution of diethyl azodicarboxylate (0.2 ml, 1.46 mmol) in THF (3 ml), and the mixture was stirred at room temperature for 40 hours. At this time, the solvent was evaporated, and the residue was taken up in 30% EtOAc in hexane. Precipitation of the product was induced by scratching with a glass rod. The white solid was collected by filtration. Analysis of the product by thin layer chromatography on silica gel indicated no triphenylphosphine oxide to be present. This intermediate (380 mg) was suspended in EtOH (20 ml), and then hydrazine monohydrate (0.1 ml, 2.07 mmol) was added. The suspension was heated at reflux for 4 hours, and the resulting colorless solution was concentrated to provide a white solid, which was purified by Chromatotron using 15% MeOH in $CHCl_3$ as the eluent to provide a pale yellow oil. The hydrochloride salt was prepared using anhydrous HCl in EtOAc, and precipitation was induced by addition of Et_2O to provide compound 6 as a tan solid (65 mg) (mp. 130-145°C, dec.): ^1H NMR ($CDCl_3$): δ 1.46 (2H, m, 2 x CH), 1.58-1.82 (11H, m, alkyl), 1.89 (2H, m CH_2), 2.22 (2H, br s, CH_2), 2.42 (2H, br s, CH_2N), 2.88 (3H, br s, NH_3), 3.54 (2H, t, J = 18.8 Hz, CH_2N), 3.62 (1H, br s, CHN), 7.48 (1H, t, J = 7.9 Hz, ArH), 7.68 (1H, d, J = 6.6 Hz, ArH), 7.88 (2H, m, ArH), 8.33 (1H, d, J = 12.5 Hz, ArH), 8.40 (1H, d, J = 1.63 Hz, ArH).

EXAMPLE 7

N-(2-Adamantyl)-5-chloro-2-naphthalenesulfonamide

Compound 7 was prepared using a procedure similar to the procedure used in Example 1. 2-Adamantanamine, 0.71 g (3.8 mmol) and 0.5 g (1.9 mmol) of 5-chloro-2-naphthalenesulfonyl chloride gave an off-white solid, 0.70 g. Recrystallization from EtOAc gave compound 7 as a yellow solid, 0.41 g (57% yield): mp 206-207°C,

^{1}H NMR ($CDCl_3$): δ 8.47 (d, J=1.8, 1 H, H1), 8.83 (d, J=8.9, 1 H, H3), 7.98 (d, J=9.0, 1H, H4), 7.88 (d, J=8.3, 1 H, H6), 7.72 (d, J=7.5, 1 H, H8), 7.52 (t, J=7.9, 1 H, H7), 5.24 (d, J=7.6, 1 H, NH), 3.50-3.45 (m, 1H, NHC<u>H</u>R), 1.83-1.51 (m, 14H, alkyl H's); anal. calcd for $C_{20}H_{22}NO_2SCl$: C, 63.90; H, 5.90; N, 3.73; found: C, 64.02; H, 5.88; N, 3.73.

EXAMPLE 8

N-((R)-(+)-2-Bornyl-5-chloro-2-naphthalenesulfonamide

Compound 8 was prepared using a procedure similar to the procedure used in Example 1. (R)-(+)-2-Bornylamine, 0.50 g (3.3 mmol) and 0.50 g (1.9 mmol) of 5-chloro-2-naphthalenesulfonyl chloride produced 0.80 g of a yellow solid. Recrystallization from isopropyl ether/methanol gave a yellow solid 0.39 g (54% yield): mp 195.6-197.6°C; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, J=1.8, 1 H, H1), 8.38 (d, J=9.0, 1 H, H3), 7.98 (d, J=9.0, 1 H H4), 7.87 (d, J=8.2, 1 H, H6), 7.72 (d, J=7.3, 1 H, H8), 7.51 (5, J=7.9, 1 H, H7), 5.03 (d, J=9.5, 1 H, NH), 3.55-3.48 (m, 1 H, NHC<u>H</u>R), 2.03-1.93 (m, 1 H, alkyl H), 1.73-1.63 (m, 1 H, alkyl H), 1.58-1.50 (m, 2 H, alkyl H's), 1.42-1.30 (m, 1H, alkyl H), 1.18-1.08 (m, 1 H, alkyl H), 0.81 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 0.74 (s, 3 H, CH_3), 0.73-0.68 (m, 1 H, alkyl H); anal. calcd. for $C_{20}H_{24}NO_2SCl$: C, 63.56; H, 6.40; N, 3.71; found: C, 63.59; H, 6.43; N, 3.76.

EXAMPLE 9

N-(1-Adamantylmethyl)-5-chloro-2-naphthalenesulfonamide

Compound 9 was prepared using a procedure similar to the procedure used in Example 1. Reaction of 0.50 ml (2.85 mmol) of 1-adamantylmethylamine and 0.50 g (1.9 mmol) of 5-chloro-2-naphthalenesulfonyl chloride yielded 0.81 g of an off-white solid. Recrystallization from chloroform gave a yellow solid,

0.41 g (55% yield): mp 204.5-206.5°C, ^{1}H NMR ($CDCl_3$): δ 8.43 (d, J=1.8, 1 H, H1), 8.40 (d, J=9.0, 1 H, H3), 7.93 (d, J=9.0, 1 H, H4), 7.89 (d, J=8.4, 1 H, H6), 7.73 (d, J=7.5, 1 H, H8), 7.53 (5, J=7.9, 1 H, H7), 4.58 (t, J=6.7, 1 H, NH), 2.61 (d, J=6.8, 2 H, $NHC\underline{H_2}R$), 1.95 (br. s, 3 H, alkyl H's), 1.72-1.68 (m, 3 H, alkyl H's), 1.60-1.55 (m, 3 H, alkyl H's), 1.482-1.45 (m, 6 H, alkyl H's); anal. calcd. for $C_{21}H_{24}NO_2SCl$: C, 64.68; H, 6.20; N, 3.59; found: C, 64.60; H, 6.23; N, 3.63.

EXAMPLE 10

N-(1-Adamantyl)-2-naphthalenesulfonamide

Compound 10 was prepared using a procedure similar to the procedure used in Example 1. The 2-naphthalenesulfonyl chloride, 0.50 g (2.2 mmol) when reacted with 0.40 g (2.6 mmol) of 1-adamantanamine gave an off-white foam. Recrystallization from isopropyl ether/methanol gave brown crystals, 0.40 g (53% yield): mp 173-176°C; ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1 H, H1), 7.98-7.88 (m, 4 H, aromatic H's), 7.65-7.58 (m, 2 H, aromatic H's), 4.73-4.65 (m, 1 H, NH), 1.95 (br. s, 3 H, alkyl H's), 1.85-1.78 (m, 6H, alkyl H's), 1.60-1.50 (m, 6 H, alkyl H's); anal. calcd. for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10; found: C, 70.22; H, 6.78; N, 4.05.

EXAMPLE 11

5-Chloro-N-(tricyclo[3.2.1.1^{3,7}]non-1-yl)-2-naphthalenesulfonamide

Compound 11 was prepared using a procedure similar to the procedure used in Example 1. Coupling 0.50 g (1.9 mmol) of 5-Chloro-2-sulfonyl chloride with 0.43 g (2.5 mmol) of 3-noradamantanamine (tricyclo[3.2.1.1^{3,7}]nonan-1-amine) gave a yellow oil. Recrystallization from isopropyl ether/methanol gave a yellow solid, 0.36 g (52% yield): mp 152-155°C; ^{1}H NMR ($CDCl_3$): δ 8.47 (d, J=1.8, 1 H, H1), 8.38 (d, J=9.0, 1

H, H3), 7.99 (d, J=9.0, 1 H, H4), 7.88 (d, J=8.3, 1 H, H6), 7.71 (d, J=7.5, 1 H, H8), 7.51 (t, J=7.9, 1 H, H7), 5.11-5.05 (m, 1 H, NH), 2.33-2.28 (m, 1 H, alkyl H), 2.18 (br. s, 2 H, alkyl H's), 1.90-1.78 (m, 7 H, alkyl H's), 1.56-1.38 (m, 3 H, alkyl H's); anal. calcd. for $C_{19}H_{20}NO_2SCl$: C, 63.06; H, 5.57; N, 3.87; found: C, 62.90; H, 5.55; N, 3.85.

EXAMPLE 12

5-Chloro-N-(3-quinuclidinyl)-2-naphthalenesulfonamide

Compound 12 was prepared using a procedure similar to the procedure used in Example 5. 3-aminoquinuclidine·2HCl, 0.5 g (2.5 mmol) and 5-chloro-2-naphthalenesulfonylchloride gave 0.60 g of a white solid. Trituration with chloroform followed by ethyl ether gave a white solid, 0.48 g (72% yield): mp 299-305°C (dec); ^{1}H NMR (DMSO d_6): δ 7.72 (d, J=1.8, 1 H, H1), 7.63 (d, J=9.0, 1 H, H3), 7.25-7.18 (m, 2 H, H4 and H6), 7.01-6.98 (m, 1 H, H8), 6.80 (t, J=7.9, 1 H, H7), 2.92-2.82 (m, 1 H, $SO_2NH\underline{CH}R$), 2.79-2.70 (m, 1 H, alkyl H), 2.45-2.24 (m, 4 H, alkyl H's), 1.41-1.27 (m, 1 H, alkyl H), 1.23-0.95 (m, 5 H, alkyl H's).

EXAMPLE 13

3-(2-Naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 13 was prepared using a procedure similar to the procedure used in Example 5. A mixture of 2-naphthalenesulfonyl chloride, 0.50 g (2.2 mmol) and 0.36 g (2.9 mmol) of 3-azabicyclo[3.2.2]nonane produced the desired product. Recrystallization from isopropyl ether/methanol gave an amber solid, 0.47 g (68% yield): mp 149-150°C; ^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1 H, H1), 7.99-7.92 (m, 3 H, aryl H's), 7.77-7.74 (m, 1 H, aryl H), 7.67-7.59 (m, 2 H, aryl H's); 3.30 (d, J=4.2, 4 H, $SO_2N(\underline{CH_2}R)_2$), 1.99 (s, 2 H, $SO_2N(CH_2\underline{CH}R)_2$), 1.73-1.57 (m, 8 H, alkyl H's); anal calcd. for

$C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; found: C, 68.67; H, 6.75; N, 4.47.

EXAMPLE 14

3-(5-Chloro-1-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 14 was prepared using a procedure similar to the procedure used in Example 5. The reaction of 0.26 g (1.0 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 0.16 g (1.3 mmol) of 3-azabicylco[3.2.2]nonane yielded an orange oil, 0.38 g. Recrystallization from hexane gave a yellow solid, 0.25 g (71% yield): mp 105-106°C; ^{1}H NMR ($CDCl_3$): 8.74 (d, J=8.6, 1 H, H8), 8.50 (d, J=8.5, 1 H, H4), 8.22 (d, J=7.4, 1 H, H2), 7.66-7.51 (m, 3 H, H3, H6 and H7), 3.39 (d, J=4.2, 4 H, $SO_2N(\underline{CH_2}R)_2$), 2.03 (s, 2 H, $SO_2N(CH_22\underline{CH}R)_2$), 1.68-1.57 (m, 8 H, alkyl H's); anal. calcd. for $C_{18}H_{20}NO_2SCl$: C, 61.79; H, 5.76; N, 4.00; found: C, 61.70; H, 5.75; N, 3.94.

EXAMPLE 15

3-(5-Chloro-2-naphthalenesulfonyl)-3-azabicyclo[3.2.1]octane

Compound 15 was prepared using a procedure similar to the procedure used in Example 5. From 0.16 g (1.1 mmol) of 3-azabicyclo[3.2.1]octane and 0.26 g (1.0 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 0.52 ml of DIEA, there was obtained 0.32 g of a cream solid. Recrystallization from isopropyl ether/methanol gave an off-white solid, 0.19 g (58% yield): mp 137-138°C; ^{1}H NMR ($CDCl_3$): δ 8.29 (d, J=9.0, 1 H, H3), 8.26 (d, J=1.6, 1 H, H1), 7.83 (d, J=8.2, 1 H, H4), 7.77 (d, J=8.9, 1 H, H6), 7.62 (d, J=7.4, 1 H, H8), 7.44 (t, J=7.9, 1 H, H7), 3.56-3.51 (m, 2 H, alkyl H's), 2.41 (d, J=10.6, 2 H, alkyl H's), 2.15 (s, 2 H, alkyl H's), 1.67-1.55 (m, 4 H, alkyl H's), 1.41-1.35 (m, 1 H, alkyl H), 1.09 (d, J=11.5, 1

H, alkyl H); anal. calcd. for $C_{17}H_{18}NO_2SCl$: C, 60.80; H, 5.40; N, 4.17; found: C, 60.74; H, 5.41; N, 4.16.

EXAMPLE 16

2-(5-Chloro-2-naphthalesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 16 was prepared using a procedure similar to the procedure used in Example 5. 4-Azahomoadamantane (2-azatricyclo[4.3.1.1^{4,8}]undecane, 0.167 g (1.1 mmol); 0.26 g (1.0 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 0.52 ml of DIEA afforded 0.40 g of pink oil. Recrystallization from isopropyl ether/methanol gave grey needles, 0.22 g (58% yield): mp 127-128°C; ^{1}H NMR ($CDCl_3$): δ 8.34 (d, J=1.6, 1 H, H1), 8.27 (d, J=8.9, 1 H, H3), 7.86 (d, J=8.9, 1 H, H4), 7.80 (d, J=8.2, 1 H, H6), 7.58 (d, J=7.3, 1 H, H8), 7.41 (t, J=7.9, 1 H, H7), 4.46 (s, 1 H, $SO_2N\underline{CH}R$), 3.43 (d, J=3.7, 2 H, $SO_2N\underline{CH_2}R$), 2.20-2.13 (m, 1 H, alkyl H), 1.82-1.72 (m, 6 H, alkyl H's), 1.41-1.33 (m, 6 H, alkyl H's); anal. calcd. for $C_{20}H_{22}NO_2SCl$: C, 63.90; H, 5.90; N, 3.73; found: C, 63.82; H, 5.91; N, 3.68.

EXAMPLE 17

2-(5-Chloro-2-naphthalenesulfonyl)-2-azaadamantane

Compound 17 was prepared using a procedure similar to the procedure used in Example 5. The 2-azaadamantane (0.05 g, 0.36 mmol) and 5-chloro-2-naphthalenesulfonyl chloride (0.09 g, 0.36 mmol) along with DIEA gave 100 mg of a yellow solid. Purification by Chromatotron using hexane/EtOAc (4:1) gave an off-white solid, 5 mg (5% yield): ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J=1.8, 1 H, H1), 8.35 (d, J=8.9, 1 H, H3), 7.99 (d, J=9.0, 1 H, H4), 7.86 (d, J=8.3, 1 H, H6), 7.68 (d, J=7.4, 1 H, H8), 7.x 48 (t, J=7.9, 1 H, H7), 4.63 (s, 1 H, alkyl H), 2.31-2.28 (m, 2 H, alkyl H's),

1.96-1.87 (m, 4 H, alkyl H's), 1.79-1.68 (m, 7 H, alkyl H's).

EXAMPLE 18

5-(5-Chloro-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 18 was prepared using a procedure similar to the procedure used in Example 5. From 0.3 g (2.0 mmol) of 2-thia-5-azabicyclo[2.2.1]heptane, 0.5 g (1.9 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 0.66 ml of DIEA there was obtained a white foam, 0.61 g. Purification by Chromatotron using hexane/EtOAc (4:1) gave a white solid, 0.21 g (32% yield): mp 161-162°C; ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1 H, H1), 8.35 (d, J=8.9, 1 H, H3), 7.93-7.87 (m, 2 H, H4 and H6), 7.67 (d, J=7.5, 1 H, H8), 7.49 (t, J=7.9, 1 H, H7), 4.73 (s, 1 H, alkyl H), 3.65 (d, J=8.3, 1 H, alkyl H), 3.54-3.50 (m, 2 H, alkyl H's), 3.10 (d, J=10.1, 1 H, alkyl H), 2.95 (d, J=10.1, 1 H, alkyl H), 1.66 (qt, J=10.7, 36.0, 2 H, alkyl H's); anal. calcd. for $C_{15}H_{14}NO_2S_2Cl$: C, 53.01; H, 4.15; N, 4.12; found: C, 52.99; H, 4.20; N, 4.07.

EXAMPLE 19

5-(5-Chloro-2-napthalenesulfonyl)-2-oxa-5-azabicyclo[2.2.1]heptane

Compound 19 was prepared using a procedure similar to the procedure used in Example 5. Reaction of 0.5 g (1.9 mmol) of 5-chloro-2-naphthalenesulfonyl chloride with 0.27 g (2.0 mmol) of 2-oxa-5-azabicyclo[2.2.1]heptane produced a white foam, 0.62 g. Recrystallization from isopropyl ether/methanol gave a yellow solid, 0.38 g (61% yield): mp 132-133°C; ^{1}H NMR ($CDCl_3$): δ 8.43 (d, J=1.2, 1 H, H1), 8.35 (d, J=8.9, 1 H, H3), 7.94 (d, J=8.9, 1 H, H4), 7.89 (d, J=8.2, 1 H, H6), 7.67 (d, J=7.4, 1 H, H8), 7.49 (t, J=7.8, 1 H, H7), 4.58 (s, 1 H, alkyl H), 4.48

(s, 1 H, alkyl H), 3.87 (d, J=7.8, 1 H, alkyl H), 3.70-3.67 (m, 1 H, alkyl H), 3.45 (d, J=9.8, 1 H, alkyl H), 3.28 (d, J-9.8, 1 H alkyl H), 1.68 (d, J=10.2, 1 H, alkyl H), 1.28 (d, J=10.2, 1 H, alkyl H); anal. calcd. for $C_{15}H_{14}NO_3SCl$: C, 55.64; H, 4.36, N, 4.33; found: c, 55.52; H, 4.40; N, 4.37.

EXAMPLE 20

2-(5-Chloro-2-naphthalenesulfonyl)-2,5-diazabicyclo[2.2.1]heptane

2-(5-Chloro-2-naphthalenesulfonyl)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo[2.2.1]heptane (0.50 g, 2 mmol) was dissolved in about 5 ml EtOAc. HCl gas was bubbled through the solution, resulting in an immediate change of color from orange to yellow. HCl gas was bubbled in for 15 minutes more and a precipitate started forming at this time. After 30 minutes, the ice bath was removed. The reaction was complete at 2 hours. The precipitate was filtered and triturated with Et_2O to give 0.37 g of compound 20 as an off-white powder, mp: 225-227°C.

EXAMPLE 21

2-(5-Chloro-2-naphthalenesulfonyl)-5-methoxycarbonyl-2,5-diazabicyclo[2.2.1]heptane

Compound 21 was prepared from compound 20 by dissolving compound 20 (0.29 g, 0.8 mmol) in 20 ml dioxane and 1 ml of 1N NaOH solution. The solution was cooled with an ice bath. Methyl chloroformate (0.062 ml, 0.8 mmol) was added dropwise. Additional 1N NaOH solution was added to keep the pH above 9. After 1 hour at room temperature, the solvent was evaporated. The residue was partitioned between chloroform and saturated sodium bicarbonate solution. The aqueous layer was extracted three times with chloroform. After drying over magnesium sulfate, the solvent was evaporated to give a yellow foam. This

was purified by Chromatotron using hexane/EtOAc (3:2) to give 0.27 g (87% yield) of a white solid: mp 151-152°C; ^{1}H NMR ($CDCl_3$): δ 8.41-8-37 (m, 2 H, H1 and H3), 7.95-7-89 (m, 2 H, H4 and H6), 7.71 (d, J=7.4, 1 H, H8), 7.53 (t, J=7.8, 1 H, H7), 4.58 (s, 1 H, alkyl H), 4.49 (s, 1 H, alkyl H), 3.68 (s, 1 H, alkyl H), 3.55-3.46 (m, 4 H, alkyl H's), 1.70 (d, J=10.1, 1 H, alkyl H), 1.33-1.28 (m, 1 H, alkyl H).

EXAMPLE 22

N-(3-Carboxy-1-adamantyl)-5-chloro-2-naphtalenesulfonamide

Compound 22 was prepared by Schotten-Baumann coupling of 5-chloro-2-naphthalenesulfonyl chloride and 3-amino-1-adamantanecarboxylic acid. Purification was achieved by basic extraction from EtOAc and precipitation with 1 N HCl gave a white solid (5% yield): mp 255-256°C; ^{1}H NMR (DMSO d_6): δ 12.02 (s, 1 H, COOH), 8.55 (s, 1 H, H1), 8.35 (d, J=8.9, 1 H, H3), 8.19 (d, J=8.2, 1 H, H4), 8.05 (d, J=9.0, 1 H, H6), 7.88-7.84 (m, 2 H, H8 and NH), 7.65 (t, J=7.9, 1 H, H7), 2.00 (s, 2 H, alkyl H's), 1.83 (s, 2 H, alkyl H's), 1.66-1.55 (in, 8 H, alkyl H's), 1.46-1.39 (m, 2 H, alkyl H's).

EXAMPLE 23

2-(5-Chloro-2-naphthalenesulfonyl)-1-hydroxy-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 23 was prepared using a procedure similar to the procedure used in Example 5. 5-Chloro-2-naphthalenesulfonyl chloride (0.091 g, 0.35 mmol), 0.055 g (0.33 mmol) of 3-hydroxy-4-azahomoadamantane (1-hydroxy-2-azatricyclo[4.3.1.1^{4,8}]undecane), along with 0.122 ml of DIEA in $CHCl_3$ gave 130 mg of a yellow solid. Purification by Chromatotron using hexane/EtOAc (3:1) gave a yellow solid, 28 mg (22% yield): mp 200-202°C; ^{1}H NMR ($CDCl_3$): δ 8.44-8.39 (m,

2 H, H1 and H3), 7.94-7.88 (m, 2 H, H6 and H8), 7.73 (d, J=7.4, 1 H, H4), 7.53 (t, J=7.9, 1 H, H7), 4.53 (s, 1 H, OH), 2.74-2.68 (m, 2 H, alkyl H's), 2.46-2.36 (m, 3 H, alkyl H's), 2.28-2.18 (m, 2 H, alkyl H's), 2.09-1.93 (m, 2 H, alkyl H's), 1.88-1.69 (m, 2 H, alkyl H's), 1.66-1.47 (m, 2 H, alkyl H's), 0.91-0.83 (m, 2 H, alkyl H's).

EXAMPLE 24

3-(5-Isoquinolinesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 24 was prepared using a procedure similar to the procedure used in Example 5. Isoquinolinesulfonyl chloride (0.5 g, 2.2 mmol), together with 0.43 g (3.3 mmol) of 3-azabicyclo[3.2.2]nonane and 1.0 ml of DIEA gave 330 mg of yellow oil. Purification by Chromatotron using chloroform/EtOAc (4:1) gave a yellow solid, 120 mg (17% yield): mp 136-137°C; ^{1}H NMR ($CDCl_3$): δ 9.34 (s, 1 H, H1), 8.68 (d, J=6.1, 1 H, H3), 8.34 (d, J=7.4, 1 H, H6), 8.19 (d, J=8.2, 1 H, H8), 7.70 (t, J=7.8, 1 H, H7), 3.41-3.38 (m, 4 H, N($\underline{CH_2}\underline{CH}$R)2), 2.08 (s, 2 H, N($CH_2\underline{CH}R)_2$) 1.70-1.61 (m, 8 H, alkyl H's).

EXAMPLE 25

5-Chloro-N-(2-oxatricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-naphthalenesulfonamide

Compound 25 was prepared using a procedure similar to the procedure used in Example 5. 0.14 g (0.50 mmol) of 5-chloro-2-naphthalenesulfonyl chloride, 0.07 g (0.46 mmol) of 1-amino-2-oxaadamantane with 0.26 ml DIEA reacted in $CHCl_3$ to produce 0.19 g of orange oil. Purification by Chromatotron using hexane/acetone/chloroform (12:1:1) gave a yellow solid, 6 mg: mp 95-97°C; ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J=1.6, 1 H, H1), 8.37 (d, J=8.9, 1 H, H3), 7.92-7.86 (m, 2 H, H4 and H6), 7.71 (d, J=7.4, 1 H, H8), 7.51 (t, J=7.4, 1 H, H7), 4.22-4.13 (m, 1 H,

alkyl H), 3.26 (qt, J=14.2, 2 H, alkyl H's), 1.30 (t, J=7.1, 4 H, alkyl H's), 1.07 (d, J=6.8, 6 H, alkyl H's).

EXAMPLE 26

N-(1-Azatricyclo[3.3.1.1^{3,7}]dec-4-yl)-5-chloro-2-naphthalenesulfonamide

Compound 26 was prepared using a procedure similar to the procedure used in Example 5. Purification by Chromatotron using chloroform/acetone/methanol (12:1:1) gave a yellow solid: ^{1}H NMR ($CDCl_3$): δ 8.60 (d, J=1.6, 1 H, H1), 8.39 (d, J=8.9, 1 H, H3), 8.06 (d, J=8.8, 1 H, H4), 7.92 (d, J=8.1, 1 H, H6), 7.74 (d, J=7.6, 1 H, H8), 7.54 (t, J=7.9, 1 H, H7), 3.44-3.40 (m, 1 H, alkyl H), 3.31-3.05 (m, 4 H, alkyl H's), 2.48 (s, 1 H, alkyl H), 2.10-1.79 (m, 6 H, alkyl H's).

EXAMPLE 27

3-(6-Quinolinesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 27 was prepared using a procedure similar to the procedure used in Example 5. 6-Quinolinesulfonyl chloride (0.48 g, 2.1 mmol), was reacted with 0.32 g (2.5 mmol) of 3-azabicyclo[3.2.2]nonane in $CHCl_3$ with DIEA, 1.1 ml, as a base. The usual work-up afforded 0.53 g of an orange oil. Purification by silica gel column chromatography using hexane/EtOAc (3:2) gave a yellow solid, 0.38 g (58% yield): mp 124-127°C; ^{1}H NMR ($CDCl_3$): δ 9.07-9.04 (m, 1 H, H2), 8.32 (d, J=1.8, 1 H, H5), 8.29 (d, J=8.6, 1 H, H3), 8.23 (d, J=8.9, 1 H, H8), 8.00 (d, J=8.9, 1 H, H7), 7.54 (d, J=8.3, 1 H, H4), 3.33 (d, J=4.2, 4 H, $N(\underline{CH_2}R)_2$), 2.10 (s, 2 H, $N(\underline{CH_2}CHR)_2$) 1.75-1.61 (m, 8 H, alkyl H's). ^{13}C NMR ($CDCl_3$): δ 150.48 (59, C9), 138.52 (333, C3), 137.20 (49, C10), 132.07 (322, C8), 129.62 (323, C5), 128.63 (109, C6), 127.61 (274, C7), 123.86 (305, C4), 56.17

(525, N($\underline{C}H_2R)_2$), 31.43 (388, N($CH_2\underline{C}HR)_2$), 25.95 (1000, other C's).

EXAMPLE 28

N-(1-Adamantyl)-6-quinolinesulfonamide

Compound 28 was prepared using a procedure similar to the procedure used in Example 5. An orange solid, 0.67 g, was obtained from the reaction of 0.43 g (1.9 mmol) of 6-quinolinesulfonyl chloride with 0.35 g (2.4 mmol) of 1-aminoadamantane. Purification by silica gel column chromatography using hexane/EtOAc (3:2) gave a yellow solid, 0.24 g (32% yield): mp 210-212°C; ^1H NMR ($CDCl_3$): δ 9.06-9.04 (m, 1 H, H2), 8.52 (d, J=1.5, 1 H, H5), 8.30 (d, J=8.3, 1 H, H3), 8.25-8.18 (m, 2 H, H7 and H 8), 7.53 (d, J=8.3, 1 H, H4), 5.62 (s, 1 H, NH), 1.98 (s, 3 H, alkyl H's), 1.85-1.80 (m, 6 H, alkyl H's), 1.58-1.50 (m, 6 H, alkyl H's).

EXAMPLE 29

2-(6-Quinolinesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 29 was prepared using a procedure similar to the procedure used in Example 5. 0.60 g of yellow solid was obtained by reacting 0.43 g (1.9 mmol) of 6-quinolinesulfonyl chloride with 0.39 g (2.5 mmol) of 2-azatricyclo[4.3.1.1^{4,8}]undecane and 1.0 ml of DIEA. Purification by silica gel column chromatography using hexane/EtOAc (3:2) gave a yellow solid, 0.36 g (55% yield): mp 143-145°C; ^1H NMR ($CDCl_3$): δ 9.06-9.04 (m, 1 H, H2), 8.42 (d, J=1.5, 1 H, H5), 8.33 (d, J=8.0, 1 H, H3), 8.23 (d, J=8.9, 1 H, H8), 8.08 (d, J=8.9, 1 H, H7), 7.55 (d, J=8.3, 1 H, H4), 4.54 (s, 1 H, N$\underline{CH}$R), 3.52 (d, J=3.6, 2 H, N$\underline{CH_2}$R), 2.28 (s, 1 H, alkyl H), 1.93-1.80 (m, 6 H, alkyl H's), 1.49-1.40 (m, 6 H, alkyl H's).

EXAMPLE 30

5-Chloro-N-(3-hydroxy-1-adamantyl)-2-naphthalenesulfonamide

Compound 30 was prepared using a procedure similar to the procedure used in Example 5. The usual reaction between 1.05 g (4 mmol) of 5-chloro-2-naphthalenesulfonyl chloride and 1.11 g (6 mmol) of the 1-amino-3-hydroxyadamantane afforded 1.4 g of a brown oil. Purification by Chromatotron using hexane/EtOAc (1:1) gave a yellow solid, 0.5 g (32% yield): mp 210-212°C; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, J='.7, 1 H, H1), 8.39 (d, J=8.9, 1 H, H3), 7.95 (d,J= 9.0, 1 H, H4), 7.89 (d, J=8.2, 1 H, H6), 7.72 (d, J=7.5, 1 H, H8), 7.52 (t, J=7.9, 1 H, H7), 4.61 (s, 1 H, NH), 2.20 (s, 2 H, alkyl H's), 1.81-1.75 (m, 6 H, alkyl H's), 1.53-1.45 (m, 6 H, alkyl H's).

EXAMPLE 31

3-(5-(9-Fluorenylmethyloxycarbonylamino)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 31 was prepared using a procedure similar to the procedure used in Example 5. Reaction of 0.69 g (1.5 mmol) of 5-(9-fluorenylmethyloxycarbonylamino)-2-naphthalenesulfonyl chloride with 0.58 g (4.5 mmol) of 3-azabicyclo[3.2.2]nonane gave 0.79 g of tan solid after work-up of the reaction. Purification by Chromatotron using dichloromethane/EtOAc (40:1) gave a yellow solid, 0.33 g (40% yield): ^{1}H NMR ($CDCl_3$): δ 7.98-7.94 (m, 1 H), 7.84-7.75 (m, 5 H), 7.65-7.55 (m, 3 H), 7.44-7.39 (m, 3 H), 7.33-7.28 (m, 2 H), 6.94 (s, 1 H, NH), 4.64-4.59 (m, 2 H, $COO\underline{CH_2}R$), 4.28 (s, 1 H, $COOCH_2\underline{CH}R$), 3.33-3.28 (m, 4 H, $N(\underline{CH_2}R)_2$), 2.09 (s, 2 H, $N(CH2\underline{CH}R)_2$), 1.72-1.55 (m, 8 H, alkyl H's).

EXAMPLE 32

3-(5-Amino-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

0.33 g (0.6 mmol) of compound 31 was dissolved in 10 ml of THF. 1.2 ml (1.2 mmol) of tetrabutylammonium fluoride (1M in THF, Aldrich) was added. After 15 minutes, the solvent was evaporated, the residue was dissolved in $CHCl_3$, and the solution was washed with brine and $NaHCO_3$ solution. The $CHCl_3$ was evaporated to an orange oil. The product was isolated as the HCl salt by treatment with HCl/EtOAc followed by trituration with diethyl ether which gave compound 32 as a tan solid, 90 mg (50% yield): ^{1}H NMR (DMSO d_6): δ 8.48-8.35 (m, 2 H), 7.80-7.70 (m, 2 H), 7.58-7.53 (m, 1 H), 6.93-6.88 (m, 1 H), 3.24-3.20 (m, 4 H, N($\underline{CH_2}$R)$_2$), 2.06 (s, 2 H, N($CH_2\underline{CH}$R)$_2$), 1.63-1.52 (m, 8 H, alkyl H's).

EXAMPLE 33

5-Chloro-N-(1-hydroxy-2-azatricyclo[4.3.1.1^{4,8}]undec-6-yl)-2-naphthalenesulfonamide

Compound 33 was prepared by first suspending compound 30 in 5 ml of chloroform. Sulfuric acid (4 ml) was added and the mixture was cooled with an ice bath. Sodium azide (0.16 g, 2.3 mmol) was added in portions over thirty minutes. After stirring at room temperature for two hours, the mixture was poured onto ice-water. The aqueous layer was made basic with 1 N NaOH solution and the product was extracted with chloroform. After drying over sodium sulfate, the solvent was evaporated to give a yellow foam. This was purified by Chromatotron using chloroform/methanol (20:1) which gave a white solid (0.23 g, 48% yield): ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J=1.7, 1 H, H1), 8.36 (d, J=9.0, 1 H, H3), 7.99 (d, J=9.0, 1 H, H4), 7.87 (d, J=8.2, 1 H, H6), 7.70 (d, J=7.4, 1 H, H8), 7.50 (t, J=7.9, 1 H, H7), 5.38 (s, 1 H, NH), 2.97-2.85 (m, 2 H,

alkyl H's), 2.18-2.02 (m, 4 H, alkyl H's), 1.90-1.78 (m, 4 H, alkyl H's), 1.67-1.63 (m, 3 H, alkyl H's), 1.48-1.42 (m, 1 H, alkyl H).

EXAMPLE 34

N-(1-Adamantyl)-1,2,3,4-tetrahydro-6-quinolinesulfonamide

Compound 34 was prepared from compound 28 following the procedure described by T.S. Hamilton and Roger Adams (J. Am. Chem. Soc., 50:2260 (1928)). 0.089 g (0.26 mmol) of compound 28 in 5 ml MeOH was hydrogenated at 40 p.s.i. overnight using 6 mg of PtO_2 catalyst. Treatment of the crude product with HCl/EtOAc gave a yellow solid, 25 mg, which was triturated with ethyl ether (30% yield). ^{1}H NMR ($CDCl_3$): δ 7.45-7.40 (m, 2 H), 6.41-6.38 (m, 1 H), 4.51 (s, 1 H, SO_2NH), 4.38 (br s, 1 H, ring NH), 3.36-3.32 (m, 2 H, alkyl H's), 2.76 (t, J=6.2, 2 H, alkyl H's), 2.00 (s, 3 H, adamantyl H's), 1.94-1.89 (m, 2 H, alkyl H's), 1.83-1.80 (in, 6 H, adamantyl H's), 1.63-1.55 (m, 6 H, adamantyl H's).

EXAMPLE 35

5-(6-Quinolinesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 35 was prepared using a procedure similar to the procedure used in Example 5. From 0.36 g (1.6 mmol) of 6-quinolinesulfonyl chloride and 0.31 g (2.0 mmol) of 5-aza-2-thiabicyclo[2.2.1]heptane there was obtained after work-up 0.42 g of an orange oil. Purification by Chromatotron using chloroform/EtOAc (4:1) gave a yellow solid, 0.23 g (47% yield): mp 141.1-143.2°C; ^{1}H NMR ($CDCl_3$): δ 9.07 (d, J=4.2, 1 H, H2), 8.41 (d, J=1.9, 1 H, H5), 8.32 (d, J=8.4, 1 H, H3), 8.24 (d, J=8.9, 1 H, H7), 8.07 (d, J=8.9, 1 H, H8), 7.56 (d, J=8.3, 1 H, H4), 4.75 (s, I H, alkyl H), 3.70-3.65 (m, 1 H, alkyl H), 3.57-

3.54 (m, 2 H, alkyl H's), 3.15-3.10 (m, 1 H, alkyl H), 3.01-2.95 (m, 1 H, alkyl H), 1.80-1.65 (m, 2 H, alkyl H's).

EXAMPLE 36

3-(1,2,3,4 Tetrahydro-6-quinolinesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 36 was prepared from compound 27 using a procedure similar to the procedure used to prepare compound 34. Compound 36 was obtained as a yellow solid (87% yield): mp 174-181°C (dec); ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J=8.2, 1 H, aryl H), 7.67-7.63 (m, 2 H, aryl H's), 3.59 (t, J=5.5, 2 H, alkyl H's), 3.25 (d, J=4.2, 4 H, N($\underline{CH_2}$R)$_2$), 2.98 (t, J=6.4, 2 H, alkyl H's), 2.33-2.25 (m, 2 H, alkyl H's), 2.10 (s, 2 H, N(CH$_2$$\underline{CH}$R)$_2$), 1.78-1.63 (m, 8 H, alkyl H's).

EXAMPLE 37

3-(1-Acetyl-1,2,3,4-tetrahydro-6-quinolinesulfonyl-3-azabicyclo[3.2.2]nonane

Compound 37 was synthesized by addition of acetyl chloride to compound 36. Compound 36 (100 mg, 0.31 mmol) was dissolved in dry tetrahydrofuran. The solution was cooled with an ice bath. Potassium *tert*-butoxide (76 mg, 0.68 mmol) was added, followed by acetyl chloride (0.03 ml, 0.41 mmol). The mixture was allowed to warm slowly to room temperature as it stirred overnight. The solvent was evaporated and the residue was extracted with EtOAc. The organics were washed with brine, dried over magnesium sulfate and evaporated to give an orange solid. Purification by Chromatotron using chloroform/EtOAc (9:1) gave compound 37 as a yellow solid (36 mg, 32% yield): mp 177-179°C; ^{1}H NMR ($CDCl_3$): δ 7.56-7.52 (m, 3 H, aryl H's), 3.80 (t, J=6.3, 2 H, alkyl H's), 3.26 (d, J=4.2, 4 H, N($\underline{CH_2}$R)$_2$), 2.82, (t, J=6.6, 2 H, alkyl H's), 2.31

(s, 3 H, CH_3), 2.10-1.97 (m, 4 H, $N(CH_2\underline{CH}R)_2$ and alkyl H's), 1.78-1.65 (m, 8 H, alkyl H's).

EXAMPLE 38

3-(4-Chloro-1-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 38 was prepared by reacting 4-chloro-1-naphthalenesulfonyl chloride (0.27 g) with 3-azabicyclo[3.2.2]nonane (0.13 g) in the presence of DIEA using a procedure similar to that used in Example 5. Yield: 0.33 g, mp: 133.9-137.3°C.

EXAMPLE 39

3-(4-Methoxy-1-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 39 was prepared by reacting 4-methoxy-1-naphthalenesulfonyl chloride (0.25 g) with 3-azabicyclo[3.2.2]nonane (0.12 g) in the presence of DIEA (0.16 g) using a procedure similar to that used in Example 5. Yield: 0.24 g, mp 167.7-169.5°C (soften 166.1°C).

EXAMPLE 40

2-(5-Chloro-1-naphthalenesulfonyl)-2-azatricyclo[4.3.1.$1^{4,8}$]undecane

Compound 40 was prepared by reacting 5-chloro-1-naphthalenesulfonyl chloride (0.21 g) with 4-azahomoadamantane (2-azatricyclo[4.3.1.$1^{4,8}$]undecane, 0.18 g) in the presence of DIEA using a procedure similar to that used in Example 5. Yield: 0.25 g, mp: 118.3-121.9°C.

EXAMPLE 41

2-(4-Methoxy-1-naphthalenesulfonyl)-2-azatricyclo[4.3.1.$1^{4,8}$]undecane

Compound 41 was prepared by reacting 4-methoxy-1-naphthalenesulfonyl chloride (0.21 g) with 4-

azahomoadamantane (2-azatricyclo[4.3.1.$1^{4,8}$]undecane, 0.20 g) in the presence of DIEA using a procedure similar to that of Example 5.

EXAMPLE 42

3-(4-Methoxy-1-naphthalenesulfonyl)-3-azabicyclo[3.2.1]octane

Compound 42 was prepared by reacting 4-methoxy-1-naphthalenesulfonyl chloride (0.27 g) with 3-azabicyclo[3.2.1]octane (0.16 g) in the presence of DIEA (0.30 g) using a procedure similar to that of Example 5. Yield: 0.34 g of a white solid, mp: 136.2-138.6°C.

EXAMPLE 43

3-(4-Methyl-1-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 43 was prepared by reacting 4-methyl-1-naphthalenesulfonyl chloride (0.69 g) with 3-azabicyclo[3.2.2]nonane (0.43 g) in the presence of DIEA using a procedure similar to that of Example 5. Yield 1.00 g of a grey solid, mp: 143.3-147.2°C.

EXAMPLE 44

5-(4-Acetoxy-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

4-Acetoxy-2-naphthalenesulfonyl chloride (375 mg, 2.50 mmol) and 5-aza-2-thiabicyclo[2.2.1]heptane (711 mg, 2.50 mmol) were combined in $CHCl_3$ (20 ml) and pyridine (20 ml) and the mixture was stirred at room temperature for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N HCl. The EtOAc was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography using 3% acetone in $CHCl_3$ to provide compound 44 as a white foam (321 mg, 35% yield): ^1H

NMR ($CDCl_3$): δ 1.60-1.79 (2H, m, CH_2), 2.48 (3H, s, CH_3CO), 2.98 (1H, dd, J = 7.78, 2.44 Hz, 1/2 CH_2), 3.18 (1H, d, J = 10.21 Hz, 1/2 CH_2), 3.51 (2H, br m, CH_2), 3.67 (1H, d, J = 9.48 Hz, CH), 4.70 (1H, s, CH), 7.61-7.70 (3H, m, ArH), 7.94-8.05 (m, 2H, ArH, 8.28 (s, 1H, ArH).

EXAMPLE 45

5-(4-Hydroxy-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane 2,2-dioxide

Compound 44 (202 mg, 0.56 mmol) was dissolved in MeOH (20 ml) and peracetic acid (228 mg, 720 mg of a 32% aqueous solution) was added. The resulting solution was stirred at room temperature for 5 hr. At this time the solvent was evaporated and the residue was partitioned between 1N HCl and $CHCl_3$. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography using 5% MeOH in $CHCl_3$ as the eluent to provide the pure compound 45 as a white foam (112 mg, 57% yield): ^1H NMR (DMSO d_6): δ 1.40 (1H, d, J = 10.06 Hz, 1/2 CH_2), 2.15 (1H, d, J = 11.47, 1/2 CH_2), 2.30 (1H, dd, J = 13.16, 2.84, CH), 2.47 (2H, s, CH_2SO_2), 2.86 (1H, d, J = 12.00 Hz, 1H, $CHSO_2$), 3.79 (1H, d, J = 4.54 Hz, 1/2 CH_2N), 4.57 (1H, s, 1/2 CH_2N), 7.11 (1H, d, J = 1.17 Hz, ArH), 7.64 (2H, m, ArH), 7.92 (1H, s, ArH), 8.07 (1H, m, ArH), 8.18 (1H, m, ArH), 8.28 (1H, s, ArH), 10.92 (1H, s, OH).

EXAMPLE 46

Methyl 1-(4-acetoxy-2-naphthalenesulfonyl)-4-benzyloxy-2-pyrrolidinecarboxylate

4-Acetoxy-2-naphthalenesulfonyl chloride (131 mg, 0.46 mmol) and O-benzyl-4-hydroxyproline methyl ester (methyl 4-benzyloxy-2-pyrrolidinecarboxylate, 108 mg, 0.46 mmol) were combined in $CHCl_3$ (20 ml) and pyridine (20 ml) and the mixture was stirred at room

temperature for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N aq HCl. The EtOAc was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography using 1% acetone in $CHCl_3$ to provide 712 mg of the compound 46 as a white foam: ^1H NMR (DMSO d_6): δ 2.16 (1H, m, 1/2 CH_2), 2.44 (1H, m, 1/2 CH_2), 2.49 (3H, s, CH_3CO), 3.64 (2H, m, CH_2N), 3.79 (3H, s, $COOCH_3$), 4.13 (1H, s, CH), 4.19 (2H, s, CH_2Ar), 4.48 (1H, t, J = 4.91 Hz, CHN), 6.90 (2H, d, J = 7.61 Hz, ArH), 7.05-7.21 (3H, m, ArH), 7.55-7.70 (2H, m, ArH), 7.75 (1H, s, ArH), 7.90 (1H, d, J = 8.05 Hz, ArH), 7.97 (1H, d, J = 7.62 Hz, ArH), 8.34 (1H, s, ArH).

EXAMPLE 47

4-Benzyloxy-1-(4-hydroxy-2-naphthalenesulfonyl)-2-pyrrolidine carboxylic acid

Methyl-1-(4-acetoxy-2-naphthalenesulfonyl)-4-benzyloxy-2-pyrrolidine carboxylate (101 mg, 0.23 mmol) was dissolved in MeOH (20 ml) and NaOH (19 mg) in water (3 ml) was added and the mixture was maintained for 3 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1N aq HCl. The $CHCl_3$ phase was dried over Na_2SO_4 then concentrated. The residue was purified by flash chromatography using 5% MeOH in $CHCl_3$. The pure compound 47 was obtained as a white foam: ^1H NMR (DMSO d_6): δ 1.61 (1H, br m, 1/2 CH_2), 2.19 (1H, br m, 1/2 CH_2), 3.22 (1H, br m, 1/2 CH_2N), 3.61 (1H, br m, 1/2 CH_2N), 4.15 (1H, br m, CHN), 4.20 (2H, s, CH_2Ar), 6.70 (1H, s, ArH), 7.01 (2H, br s, ArH), 7.09-7.21 (3H, m, ArH), 7.25-7.48 (3H, m, ArH), 7.69 (1H, d, J = 8.15, ArH), 8.27 (1H, d, J = 8.07, ArH).

EXAMPLE 48

3-(5-Acetoxy-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

The 5-acetoxy-2-naphthalenesulfonyl chloride was prepared by acylating 0.30 g (1.25 mmol) of 5-hydroxy-2-naphthalenesulfonic acid with acetic anhydride and pyridine in a manner similar to the reference example. The 5-acetoxy-2-sulfonic acid was then treated with $POCl_3$ yielding an orange oil, 0.26 g. The oil was reacted with 0.12 g (0.96 mmol) of 3-azabicyclo[3.2.2]nonane in $CHCl_3$ solution. The usual work-up gave 270 mg of a green oil. Purification by Chromatotron using hexane/acetone/chloroform (8:1:1) gave a yellow oil, 75 mg (22% yield): ^1H NMR ($CDCl_3$): δ 8.34 (d, J=1.5, 1 H, H1), 7.99 (d, J=8.9, 1 H, H3), 7.87 (d, J=8.4, 1 H, H6), 7.78 (d, J=8.9, 1 H, H4), 7.60 (t, J=8.0, 1 H, H7), 7.40 (d, J=7.6, 1 H, H8), 3.29 (d, J=4.2, 4 H, N($\underline{CH_2}$R)$\underline{2}$), 2.50 (s, 3 H, CH_3), 2.08 (s, 2 H, N($CH_2\underline{CH}$R)$_2$) 1.74-1.61 (m, 8 H, alkyl H's).

EXAMPLE 49

3-(5-Hydroxy-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 49 was prepared from compound 48, by dissolving compound 48 in 3 ml THF and then adding 2 ml water and 2 ml saturated sodium bicarbonate solution. After stirring overnight, the solvent was evaporated and the product extracted with chloroform. After drying over magnesium sulfate, the solvent was evaporated to give an orange oil. This was purified by Chromatotron using hexane/EtOAc (3:1) which gave a yellow solid (32 mg, 48% yield): ^1H NMR ($CDCl_3$): δ 8.33 (d, J=8.8, 1 H, H3), 8.25 (d, J=1.6, 1 H, H1), 7.70 (d, J=8.8, 1 H, H4), 7.49 (d, J=8.3, 1 H, H6), 7.40 (t, J=7.8, 1 H, H7), 7.02 (d, J=7.4, 1 H, H8), 6.68 (br s, 1 H, OH), 3.30 (d, J=4.2, 4 H, N($\underline{CH_2}$R)2),

2.08 (s, 2 H, N($CH_2\underline{CH}R)_2$),1.72-1.58 (in, 8 H, alkyl H's).

EXAMPLE 50

5-Acetoxy-N-(1-adamantyl)-2-naphthalenesulfonamide

Compound 50 was prepared using a procedure similar to the procedure used in Example 5. 0.61 g (4.0 mmol) of 1-adamantanamine and 0.50 g (2.0 mmol) of 5-acetoxy-2-naphthalenesulfonyl chloride gave 0.78 g of a green foam. Purification by Chromatotron using hexane/EtOAc (2:1) gave a green solid, 0.18 g (25% yield): mp 247-249°C; ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J=1.8, 1 H, H1), 8.30 (d,J=8.9, 1 H, H3), 7.84 (d, J=9.0, 1 H, H4), 7.54 (d, J=8.1, 1 H, H6), 7.42 (t, J=7.9, 1 H, H7), 6.95 (d, J=7.6, 1 H, H6), 5.45 (s, 1 H, NH), 1.99 (s, 3 H, alkyl H's), 1.82-1.79 (m, 6 H, alkyl H's), 1.54-1.50 (m, 9 H, alkyl H's and CH_3). Anal. calcd. for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.71; H, 6.49; N, 3.81.

EXAMPLE 51

3-(4-Acetoxy-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

4-Acetoxy-2-naphthalenesulfonyl chloride (861 mg, 3.02 mmol) and 3-azabicyclo[3.2.2]nonane (379 mg, 3.02 mmol) were combined in $CHCl_3$ (20 ml) and pyridine (20 ml) and the mixture was stirred at room temperature for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N HCl. The EtOAc was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography using 1% acetone in $CHCl_3$ to provide the pure compound 51 as a white foam (712 mg, 63% yield): ^{1}H NMR ($CDCl_3$): δ 1.52-1.84 (8H, m, 4 x CH_2), 2.02-2.13 (2H, br s, 2 x CH), 2.46 (3H, s, CH_3CO), 3.31 (4H, d, J

= 4.2 Hz, 2 x CH_2), 7.56-7.71 (3H, m, ArH), 7.92-8.02 (2H, m, ArH).

EXAMPLE 52

3-(4-Hydroxy-2-naphthalenesulfonyl)-3-azabicyclo-[3.2.2]nonane

Compound 51 (637 mg, 1.70 mmol) was dissolved in MeOH (20 ml) and KOH (150 mg) in water (3 ml) was added and the mixture was maintained for 1 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1N aq HCl. The $CHCl_3$ phase was dried over Na_2SO_4 then concentrated. The residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure compound 52 was obtained as a pink foam (412 mg, 73% yield): ^{1}H NMR ($CDCl_3$): δ 1.53-1.89 (8H, m, 4 x CH_2), 2.02 (2H, br s, 2 x CH), 3.28 (4H, d, J = 4.16 Hz, 2 x CH_2), 7.31 (1H, s, ArH), 7.58-7.68 (2H, m, ArH), 7.85-7.98 (2H, m, ArH), 8.27-8.36 (1H, m, ArH).

EXAMPLE 53

2-(4-Acetoxy-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

4-Acetoxy-2-naphthalenesulfonyl chloride (480 mg, 1.69 mmol) and 4-azahomoadamantane (2-azatricyclo[4.3.1.1^{4,8}]undecane, 255 mg, 1.69 mmol) were combined in $CHCl_3$ (20 ml) and pyridine (20 ml) and the mixture was stirred at room temperature for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N HCl. The EtOAc was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography using 3% acetone in $CHCl_3$ to provide the pure product compound 53 as a white foam (273 mg, 67% yield): ^{1}H NMR ($CDCl_3$): δ 1.46-1.58 (7H, m, alkyl), 1.73-1.98 (8H, m, alkyl), 2.23 (1H, br m, 1H), 2.50 (3H, s, CH_3CO), 3.52

(2H, d, 3.63 Hz, CH_2), 4.51 (1H, br m, CH), 7.60-7.72 (3H, m, ArH), 7.89-8.01 (2H, m, ArH), 8.27 (1H, s, ArH).

EXAMPLE 54

2-(4-Hydroxy-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 53 (161 mg, 0.40 mmol) was dissolved in MeOH (20 ml) and KOH (113 mg) in water (3 ml) was added and the mixture was maintained for 1 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1N HCl. The $CHCl_3$ phase was dried over Na_2SO_4, then concentrated. The residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure product was obtained as a pink foam (98 mg, 68% yield): ^{1}H NMR ($CDCl_3$): δ 1.23-1.62 (7H, m, alkyl), 1.64-1.98 (8H, m, alkyl), 2.21 (1H, br s, CH), 3.54 (2H, d, J = 3.63 Hz, CH_2), 4.49 (1H, br m, CH), 7.25-7.38 (1H br s, OH), 7.38 (1H, d, J = 1.29 Hz, ArH), 7.51-7.70 (2H, m, ArH), 7.86-8.01 (2H, m, ArH), 8.25-8.38 (1H, m, ArH).

EXAMPLE 55

5-(4-Hydroxy-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 44 (207 mg, 0.57 mmol) was dissolved in MeOH (20 ml) and KOH (160 mg) in water (3 ml) was added and the mixture was maintained for 1 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1N HCl. The $CHCl_3$ phase was dried over Na_2SO_4, then concentrated. The residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure product compound 55 was obtained as a white foam (173 mg, 92% yield): ^{1}H NMR (DMSO d_6): δ 1.35 (1H, d, J = 10.57, 1/2 CH_2), 1.57 (1H, d, J = 10.48, 1/2 CH_2),

2.83-3.02 (2H, m, CH_2), 3.24-3.51 (2H, m, CH_2), 3.61 (1H, s, CH), 4.58 (1H, s, CH), 7.14 (1H, s, ArH), 7.61 (2H, m, ArH), 7.90 (1H, s, ArH), 8.06 (1H, m, ArH), 8.17 (1H, m, ArH), 10.87 (1H, br s, OH).

EXAMPLE 56

3-(4-(3-Pyridylmethyloxy)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 52 (147 mg, 0.44 mmol), 3-picolylchloride hydrochloride (73 mg, 0.44 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (44 mg, 1.1 mmol, a 60% dispersion in oil) was added and the mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between 1N KOH and $CHCl_3$. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure compound 56 was obtained as a tan foam (124 mg, 66% yield): ^{1}H NMR ($CDCl_3$): δ 1.53-1.76 (8H, m, 4 x CH_2), 2.06 (2H, s, 2 x CH), 3.21 (4H, d, J = 4.19 Hz, 2 x CH_2), 5.34 (2H, s, CH_2Ar), 7.12 (1H, s, ArH), 7.37 (1H, m, ArH), 7.64 (2H, m, ArH), 7.82-7.98 (3H, m, ArH), 8.35 (1H, m, ArH), 8.62 (1H, m, ArH), 8.80 (1H, m, ArH).

EXAMPLE 57

3-(4-Carboxymethyloxy-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 52 (117 mg, 0.35 mmol), α-bromomethylacetate (54 mg, 0.35 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (44 mg, 1.1 mmol, a 60% dispersion in oil) was added and the mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N HCl. The EtOAc phase was dried (Na_2SO_4) and

concentrated and the residue was purified by flash chromatography using 30% EtOAc in hexane. The pure product was obtained as a white foam, 51 mg (86% yield): ^{1}H NMR ($CDCl_3$): δ 1.52-1.81 (8H, m, 4 x CH_2), 2.06 (2H, br s, 2 x CH), 3.34 (4H, 2 x CH_2), 3.83 (3H, s, $COOCH_3$), 4.94 (2H, s, OCH_2), 6.98 (1H, s, ArH), 7.61 (m, 2H, ArH), 7.94 (m, 2H, ArH), 8.82 (1H, d, J = 5.7 Hz, ArH). This material (62 mg, 0.15 mmol) was dissolved in MeOH (10 ml) and KOH (50 mg) in H_2O (2 ml) was added. The mixture was stirred for 3 hr then the solvent was evaporated and the residue was partitioned between 1N HCl and $CHCl_3$. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 10% MeOH in $CHCl_3$ to provide the pure product (51 mg, 86%) as a white foam: ^{1}H NMR ($CDCl_3$): δ 1.21-1.68 (8H, m, 4 x CH_2), 1.71-1.94 (2H, br s, 2 x CH_2), 3.31 (4H, m, 2 x CH_2), 4.52 (2H, br s, OCH_2), 6.99 (1H, s, ArH), 7.24 (2H, m, ArH), 7.61 (2H, m, ArH), 8.14 (1H, br s, ArH).

EXAMPLE 58

3-(4-(3-(4-*tert*-Butoxycarbonyl-1-piperazinyl)propyloxy)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 52 (200 mg, 0.60 mmol), 1-(3-chloropropyl)piperazine dihydrochloride monohydrate (158 mg, 0.60 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (35 mg, 0.9 mmol, a 60% dispersion in oil) was added and the mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1N HCl. The EtOAc phase was washed with satd. aq $NaHCO_3$ then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 2% MeOH in $CHCl_3$ to provide compound 58 as a white foam (212 mg, 63% yield): ^{1}H NMR ($CDCl_3$): δ 1.46 (9H, s, t-Bu), 1.47-1.58 (8H, m, 4

x CH_2), 2.0-2.15 (2H, br s, 2 x CH), 2.45 (2H, m, CH_2), 2.48 (4H, br s, 2 x CH_2), 2.65 (2H, t, J = 7.02 Hz, CH_2N), 3.33 (4H, d, J = 4.19 Hz, 2 x CH_2), 3.47 (2H, t, J = 4.24 Hz, CH_2O), 7.05 (1H, s, ArH), 7.27 (1H, s, ArH), 7.58-7.73 (2H, m, ArH), 7.85-7.92 (2H, m, ArH), 8.26-8.35 (1H, m, ArH).

EXAMPLE 59

3-(4-(3-(1-Piperazinyl)propyloxy)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 58 (92 mg, 0.16 mmol) was dissolved in MeOH (30 ml) and a solution of anhydrous HCl in MeOH (5 ml) was added. The solution was stirred at room temperature for 3 hr. At this time the solvent was evaporated under reduced pressure to provide a white foam of compound 59 as a HCl salt (87 mg, 100% yield): ^1H NMR ($CDCl_3$): δ 1.51-1.85 (8H, m, 4 x CH_2), 2.12 (2H, br s, 2 x CH), 2.47 (2H, br m, CH_2), 2.60 (2H, br s, CH_2N), 3.25-3.72 (8H, br s, 4 x CH_2), 4.48 (2H, br s, CH_2O), 7.12 (s, 1H, ArH), 7.77 (2H, m, ArH), 8.05 (1H, s, ArH), 8.22 (1H, m, ArH), 8.38 (1H, m, ArH), 9.98 (2H, br s, NH_2).

EXAMPLE 60

3-(4-(2-Dimethylamino)ethyloxy)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 52 (117 mg, 0.35 mmol), 2-dimethylaminoethyl chloride hydrochloride (51 mg, 0.35 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (21 mg, a 60% dispersion in oil) was added and the mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1N KOH. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 8% MeOH in $CHCl_3$ to provide compound 60 as a white foam (84 mg, 59% yield): ^1H NMR

($CDCl_3$): δ 1.42-1.80 (8H, m, 4 x CH_2), 2.14 (2H, s, 2 x CH), 2.45 (6H, s, 2 x CH_3N), 2.96 (2H, t, J = 5.53 Hz, CH_2), 3.30 (4H, d, J = 4.2 Hz, 2 x CH_2N), 4.32 (2H, t, J = 5.56 Hz, CH_2), 7.06 (1H, s, ArH), 7.51-7.63 (2H, m, ArH), 7.85-7.94 (2H, m, ArH), 8.28 (1H, d, J = 8.95 Hz, ArH).

EXAMPLE 61

2-(4-(3-Pyridylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 54 (77 mg, 0.21 mmol), 3-picolylchloride hydrochloride (42 mg, 0.21 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (41 mg, 1.1 mmol, a 60% dispersion in oil) was added and the mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between 1N KOH and $CHCl_3$. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure product compound 61 was obtained as a tan foam (52 mg, 54% yield): ^{1}H NMR ($CDCl_3$): δ 1.25-1.59 (7H, m, alkyl), 1.65-1.98 (8H, m, alkyl), 2.21 (1H, s, CH), 3.45 (2H, d, J = 3.74 Hz, CH_2), 4.48 (1H, br m, CH), 7.20 (1H, d, J = 1.37 Hz, ArH), 7.39 (1H, m, ArH), 7.64 (2H, m, ArH), 7.85-7.89 (m, 3H, ArH), 8.01 (1H, s, ArH), 8.30-8.39 (1H, m, ArH), 8.65 (1H, dd, J = 6.21, 1.35 Hz, ArH), 8.82 (1H, s, ArH).

EXAMPLE 62

5-(4-(3-Pyridylmethyloxy)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 55 (66 mg, 0.20 mmol), 3-picolylchloride hydrochloride (40 mg, 0.20 mmol) and a crystal of KI were combined in DMF (30 ml). Sodium hydride (41 mg, 1.1 mmol, a 60% dispersion in oil) was added and the

mixture was stirred at 90°C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between 1N KOH and $CHCl_3$. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography using 5% acetone in $CHCl_3$. The pure compound 62 was obtained as a tan foam (49 mg, 58% yield): ^1H NMR ($CDCl_3$): δ 1.52 (1H, d, J = 10.57 Hz, 1/2 CH_2), 1.69 (1H, J = 10.74 Hz, 1/2 CH_2), 1.81 (1H, br s, CH), 2.91 (1H, dd, J = 10.12, 2.53, 1/2 CH_2), 3.09 (1H, d, J = 10.15 Hz, 1/2 CH_2), 3.50 (2H, m, CH_2), 3.61 (1H, dd, J = 10.21, 1.14 Hz, CH), 4.62 (2H, s, CH_2Ar), 7.19 (1H, d, J = 1.39 Hz, ArH). 7.39 (1H, dd, J = 11.61, 4.87 Hz, 7.60-7.69 (2H, m, ArH), 7.82-7.98 (2H, m, ArH), 8.01 (1H, s, ArH), 8.30-8.38 (1H, m, ArH), 8.68 (1H, dd, J = 10.19, 1.35 Hz, ArH), 8.81 (1H, d, J = 1.86 Hz, ArH).

EXAMPLE 63

2-(4-(2-Methyl-3-pyridylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 63 was prepared by stirring a mixture of compound 54 (0.3 g, 0.83 mmol), 2-methyl-3-picolyl chloride (0.24 g, 1.7 mmol) and CS_2CO_3 (0.97 g, 2.97 mmol) in DMF (10 mL) at room temperature for 18 h. Usual workup followed by purification by Chromatotron using hexane/EtOAc/CH_2Cl_2 6:1:1 as the eluent gave the compound as a gum. This was further purified by crystallization from EtOAc/hexane to give 0.28 g of a solid, mp. 138-141°C.

EXAMPLES 64-1 and 64-2

64-1. 2-(5-Benzyloxycarbonylamino-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

64-2. 2-(5-Amino-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Preparation of 5-Benzyloxycarbonylamino-2-naphthalenesulfonyl chloride.

5-Amino-2-naphthalene sulfonic acid (5.00 g, 22.3 mmol), carbobenzyloxy chloride (3.5 ml, 24.6 mmol), and DIEA (12.5 ml, 78.4 mmol) were combined in DMF (100 ml) and the mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with 1N HCl and the $CHCl_3$ phase was dried (Na_2SO_4) and concentrated. The residue was triturated with Et_2O and again concentrated to provide a purple foam (7.01g, 87%). This material was used in the next step without further purification. The above product was dissolved in CH_2Cl_2 (50 ml) and phosphorous pentachloride (1.41 g, 6.72 mmol) was added. The mixture was stirred at room temperature for 16 h. At this time the mixture was passed through a plug of silica gel and the filtrate was concentrated to provide an off white solid (7.50 g, 71%): 1H NMR ($CDCl_3$): δ 5.30 (2H, s, -OCH2Ar), 7.37-7.41 (2H, m, 2 x ArH), 7.24 (1H, t, J = 7.8 Hz, ArH), 7.80 (1H, d, J = 4.5 Hz, ArH), 7.93 (1H, d, 6.9 Hz, ArH), 8.04 (1H, d, 6.1 Hz, ArH), 8.54 (1H, br s, -NHCO-).

5-Benzyloxycarbonylamino-2-naphthalenesulfonyl chloride (1.01 g, 2.93 mmol), 4-azahomoadamantane(2-azatricyclo[4.3.1.1^{4,8}]undecane) (500 mg, 2.66 mmol), and DIEA (1.7 ml, 10.26 mmol) were combined in CH_2Cl_2 (50 ml) and stirred at room temperature for 16 h. At this time the solvent was distilled and the residue was partitioned between saturated aq Na_2CO_3 and CH_2Cl_2. The CH_2Cl_2 phase was dried (Na_2SO_4) and filtered through a silica plug. The filtrate was concentrated and the product was further purified by Chromatotron using (hexane/EtOAc 4:1) to provide the compound 64-1 as a white solid 1.20 g (92.0%): ^{1}H NMR ($CDCl_3$): δ 1.27-1.49 (6H, m, alkyl), 1.64-1.89 (6H, m, alkyl), 2.15 (1H, br s, -CH-), 3.41 (2H, d, J = 3.6 Hz, -CH_2N-), 4.42 (1H, br m. -CHN-), 5.21 (2H, s, -OCH_2Ph), 7.21-7.49 (6H, m, 5 x ArH), 7.64 (2H, m, 2 x ArH),

7.75 (s, 1H, ArH), 7.85 (1H, br d, J = 6.9 Hz, ArH), 7.96 (1H d, J = 9.0 Hz, ArH), 8.25 (1H, d, J = 1.2 Hz, ArH); ESMS (*m/z*) 491 (MH^+); Anal. calcd for $C_{28}H_{30}N_2O_4S$: C, 68.55; H, 6.16; N, 5.71; S 6.53; found: C, 68.37; H, 6.22; N, 5.68; S, 7, 6.50.

The above compound 64-1 (0.96 g, 1.97 mmol) was dissolved in EtOAc (50 ml) and a catalytic amount of palladium on carbon (10%, 0.100 g) was added. The mixture was stirred under an atmosphere of hydrogen for 18 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated and the residue was purified by Chromatotron using hexane/EtOAc/MeOH (50:50:2) as solvent to provide compound 64-2 as a yellow solid (587 mg, 83%): ^{1}H NMR ($CDCl_3$): δ 1.32-1.49 (6H, m, alkyl), 1.68-1.90 (6H, m, alkyl), 2.19 (1H, br m, -CH-), 3.47 (2H, d, J = 3.6 Hz, CH_2N), 4.38 (2H, br s, NH_2), 4.46 (1H, br m, CHN), 6.82-6.90 (1H, m, ArH), 7.31-7.38 (2H, m, 2 x ArH), 7.70 (1H, dd, J = 8.7, 2.0 Hz, ArH), 7.91 (1H, d, J = 9.0 Hz, ArH), 8.28 (1H, d, J = 1.8 Hz, ArH); ESMS (*m/z*) 357 (MH^+); Anal. calcd for $C_{28}H_{30}N_2O_4S$: C, 67.39; H, 6.79; N, 7.86; S, 8.99; found: C, 67.33; H, 6.82; N, 7.85; S, 8.92.

The following compounds were prepared in a fashion analogous to the preparation of compounds 64-1 and 64-2 by substituting the requisite amine in place of 4-azahomoadamantane.

EXAMPLES 65-1 and 65-2

65-1. 5-(5-Benzyloxycarbonylamino-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

65-2. 5-(5-Amino-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1] heptane

Compound 65-1 was prepared from 5-benzyloxycarbonylamino-2-naphthalenesulfonyl chloride (4.00 g, 18.13 mmol), 5-aza-2-thiabicyclo[2.2.1]heptane (2.50 g, 16.48 mmol) and DIEA (9.50 ml, 57.68 mmol) in

100 ml of CH_2Cl_2. Purification by flash chromatography using hexane/EtOAc (2:1) as the eluent gave a yellow solid (4.31 g, 57.2%): ^1H NMR ($CDCl_3$): δ 1.48 (1H, d, 9.3 Hz, alkyl), 1.62 (1H, d, 9.3 Hz, alkyl), 2.90 (1H, d, 10 Hz, alkyl), 3.07 (1H, d, 10.2 Hz, alkyl), 3.39-3.42 (2H, m, alkyl), 3.57 (1H, d, 8.4 Hz, alkyl), 4.60 (1H, br s, -NC<u>H</u>-), 5.22 (2H, s, -COOC<u>H</u>$_2$Ar), 6.89 (1H, d, 6.6 Hz, ArH), 7.31-7.40 (5H, m, 5 x ArH), 7.46-7.55 (2H, m, ArH), 7.69 (2H, d, 9.0 Hz, ArH), 7.90 (1H, d, 6.9 Hz, ArH), 7.96 (1H, d, 9.0 Hz, ArH), 8.20 (1H, s, ArH); ESMS (*m/z*) 472 ([M+NH$_4$]$^+$); Anal. Calcd for $C_{23}H_{22}N_2O_4S_2$: C, 60.77; H, 4.88; N, 6.16; S, 14.11. Found: C, 60.49; H, 4.89; N, 6.05; S, 13.96.

A mixture of the above compound 65-1 (3.25 g, 4.37 mmol), 10 ml of anisole and 5 ml of $(CH_3)_2S$ was added into a 100 ml Teflon HF container and cooled with liquid N_2. 50 ml of HF was added to the solution and the mixture was stirred for 1h and concentrated. The reaction mixture was triturated with ether (20 ml) and the residue was redissolved in 75 ml of EtOAc. The solution was extracted with satd. Na_2CO_3 (2 x 75ml), filtered though a silica plug (20 g) and concentrated. Purification of the residue by flash chromatography using CH_2Cl_2/MeOH (5:1) as an eluent provided compound 65-2 as a yellow solid (1.38 g, 60.3%): ^1H NMR ($CDCl_3$): δ 1.50 (1H, d, 9.3 Hz, alkyl), 1.62 (1H, d, 9.3 Hz, alkyl), 2.90 (1H, d, 10 Hz, alkyl), 3.07 (1H, d, 10.2 Hz, alkyl), 3.43-3.46 (2H, m, alkyl), 3.61 (1H, d, 8.4 Hz, alkyl), 4.46 (2H, br s, ArNH$_2$), 4.65 (1H, br s, -C<u>H</u>N-), 6.89 (1H, d, 6.6 Hz, ArH), 7.34-7.37 (2H, m, ArH), 7.69 (1H, d, 8.7 Hz, ArH), 7.94 (1H, d, 9.0 Hz, ArH), 8.29 (1H, br s, ArH); ESMS (*m/z*) 338 ([M+NH$_4$]$^+$).

EXAMPLES 66-1 and 66-2

66-1. N-(1-Adamantyl)-5-benzyloxycarbonylamino-2-napthalene sulfonamide

66-2. N-(1-Adamantyl)-5-amino-2-

naphthalenesulfonamide

Compound 66-1 was prepared from 5-benzyloxycarbonylamino-2-naphthalenesulfonyl chloride (4.72g, 12.56 mmol), 1-aminoadamantane (2.08 g, 13.81 mmol) and DIEA (7.20 ml, 43.98 mmol) in 75 ml of CH_2Cl_2. Purification by flash chromatography using hexane/EtOAc (4:1) as an eluent gave a white solid (2.14 g, 39.7%): ^{1}H NMR (CD_3OD): δ 1.44-1.48 (6H, m, alkyl), 1.70 (6H, br s, alkyl), 1.88 (3H, br s, alkyl), 5.21 (2H, s, -OC<u>H</u>$_2$Ar), 7.35-7.46 (5H, m, ArH), 7.60-7.66 (2H, m ArH), 7.74 (1H, d, J = 8.4 Hz, ArH), 7.91 (1H, d, J = 9.34 Hz, ArH), 7.98 (1H, d, J = 8.4 Hz, ArH), 8.24 (1H, d, J = 9.3 Hz, ArH), 8.44 (1H, br s, ArH), 9.79 (1H, br s, SO_2N<u>H</u>-); ESMS (*m/z*) 508 ($[M+NH_4]^+$).

The above compound 66-1 (2.14 g, 4.37 mmol) was dissolved in MeOH (50 ml) and hydrogenated in the presence of a catalytic amount (100 mg) of palladium on carbon (10%). Usual workup followed by purification by Chromatotron using CH_2Cl_2/MeOH (5:1) provided compound 66-2 as a yellow solid (996 mg, 63.9%): ^{1}H NMR (CD_3OD): δ 1.44 (6H, m, alkyl), 1.70 (6H, br s, alkyl), 1.87 (3H, br s, alkyl), 5.97 (2H, br s, $ArNH_2$), 6.81 (1H, d, J= 7.2 Hz, ArH), 7.35-7.56 (2H, m, ArH), 7.56 (1H, br s, -**SO_2N<u>H</u>**), 7.69 (1H, dd, J = 3.3, 1.5 Hz, ArH), 8.21 (2H, q, J = 1.5 Hz, ArH);

EXAMPLE 67

5-Chloro-N-(2-hydroxy-1,7,7-trimethyl bicyclo[2.2.1]hept-3-yl)-2-nephthalenesulfonamide

Compound 67 was prepared according to a procedure similar to that described for preparing compound 5. A mixture of
3-amino-1,7,7-trimethylbicyclo[2.2.1]hept-2-ol (Tanaka, K. et al., <u>J. Chem. Soc. Perkin Trans 1</u> <u>6</u>: 1445-1452 (1991)) (0.25g, 1.47 mmol), 5-chloro-2-naphthalenesulfonyl chloride (0.42 g, 1.63 mmol) in CH_2Cl_2 (50 ml) and DIEA (0.22 ml, 4.41 mmol) was stirred for 18 h. Usual workup followed by purification by

Chromatotron using hexane/EtOAc (4:1) as an eluent gave a white solid (0.38 g, 62.4%). ^{1}H NMR (CD_3OD): δ 1.46 (3H, s, Me), 1.55 (3H, s, Me), 1.65 (1H, d, J = 18 Hz, alkyl), 1.77 (3H, s, Me), 2.09 (1H, t, J = 10.2 Hz, alkyl), 2.29 (1H, m, alkyl), 2.45 (1H, d, J = 4.2 Hz, alkyl), 3.88 (1H, q, J = 3.3 Hz, alkyl), 4.18 (1H, t, J = 6.6 Hz, alkyl), 8.46 (1H, t, J = 7.5 Hz, ArH), 8.70 (1H, d, J = 7.5 Hz, ArH), 8.84 (1H, d, J = 8.7 Hz, ArH), 9.00 (1H, d, J = 7.6 Hz, ArH), 9.12 (1H, d, J = 9.0 Hz, ArH), 9.37 (1H, s, ArH).

EXAMPLE 68

2-(5-(3-Pyridylacetylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

The amine compound 64-2 (125 mg, 0.32 mmol), 3-pyridylacetic acid (60.7 mg, 0.35 mmol), BOP reagent (148 mg, 0.35 mmol), and DIEA (0.2 ml, 1.02 mmol) were combined in THF (30 ml) and the solution was stirred at room temperature for 18 h. At this time the solvent was evaporated and the residue was partitioned between EtOAc and satd. aq Na_2CO_3. The EtOAc layer was washed with satd. aq LiCl, dried (Na_2SO_4), and concentrated. The residue was purified by Chromatotron using hexane/EtOAc (4:1) as an eluent to provide compound 68 as a white solid (0.44g, 27 %): ^{1}H NMR ($CDCl_3$): δ 1.41-1.49 (6H, m, alkyl), 1.77-1.91 (6H, m, alkyl), 2.27 (1H, br s, CH), 3.48 (2H, d, J = 3.2 Hz, CH_2N), 4.49 (1H, br t, J = 6.0 Hz, CHN), 5.13 (2H, s, COC$\underline{H_2}$Ar), 7.10 (1H, br s, -NHCO), 7.35-7.45 (4H, m ArH), 7.58 (1H, t , J = 8.1 Hz, ArH), 7.76-7.82 (2H, m, Ar), 7.97 (2H, br d, J = 8.7 Hz, ArH), 8.36 (1H, d , J = 1.8 Hz, ArH).

EXAMPLE 69

2-(5-(2-Pyrazinylcarbonylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 69 was prepared using a procedure similar to that of Example 68. A mixture of 0.13 g (0.38 mmol)

of the amine (Compound 64-2), 0.048 g, (0.39 mmol) of 2-pyrazine carboxylic acid, 0.22 ml of DIEA and 0.16 g (0.39 mmol) of BOP afforded a yellow solid. Purification by Chromatotron using hexane/EtOAc (4/1) gave a white solid, 85 mg (51 %).: ^{1}H NMR ($CDCl_3$): δ 1.39-1.57 (6H, m, alkyl), 1.76-1.97 (6H, m, alkyl), 2.25 (1H, br s, CH), 3.50 (2H, d, J = 3.9 Hz, CH_2N), 4.51 (1H, br t, J = 5.1 Hz, CHN), 7.67 (1H, t, J = 7.8 Hz, ArH), 7.85 (1H, d, J = 8.1 Hz, ArH), 7.91 (1H, dd, J = 8.7, 1.8 Hz, ArH), 8.13 (1H, d, J = 8.7 Hz, ArH), 8.42 (2H, m, 2 x ArH), 8.70 (1H, m, ArH), 8.89 (1H, d, J = 2.4 Hz, ArH), 9.57 (1H, d, J = 1.5 Hz, ArH), 10.32 (1H, br s, NH); ESMS (*m/z*) 463 (MH^+); Anal. calcd for $C_{25}H_{26}N_4O_3S$: C, 64.92; H, 5.67; N, 12.11; S, 6.93; found: C, 64.94; H, 5.70; N, 12.14; S, 6.99.

EXAMPLE 70

2-(5-(5-Methyl-2-pyrazinylcarbonylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

The amine (compound 64-2, 100 mg, 0.28 mmol), 5-methyl-2-pyrazinecarboxylic acid (46 mg, 0.34 mmol), BOP reagent (148 mg, 0.34 mmol), and DIEA (0.16 ml, 1.02 mmol) were combined in THF (30 ml) and the solution was stirred at room temperature for 18 h. At this time the solvent was evaporated and the residue was partitioned between EtOAc and saturated aqueous Na_2CO_3. The EtOAc layer was washed with saturated aqueous LiCl, dried (Na_2SO_4), and concentrated. The residue was purified by Chromatotron using hexane/EtOAc (4:1) as an eluent to provide compound 70 as a white solid (0.13 g, 98 %). mp 224-225 °C. ^{1}H NMR ($CDCl_3$): δ 1.41-1.49 (6H, m, alkyl), 1.68-1.90 (6H, m, alkyl), 2.43 (1H, br m, CH), 2.73 (3H, s, Me), 3.50 (2H, d, J= 3.6 Hz, C<u>H</u>2N), 4.51 (1H, br m, NC<u>H</u>(CH_2-)$_3$), 7.62 (1H, t, $J_{1,2}$ =7.8, ArH), 7.89 (2H, q, J = 9.3 Hz, ArH), 8.12 (1H, d, J = 9.0 Hz, ArH), 8.41-8.44 (2H, m, ArH), 8.54 (1H, b s ArH), 9.41 (1H, b s, ArH), 10.28 (1H, b s, -CON<u>H</u>-), ESMS (*m/z*) 494 ($[M+NH_4]^+$); Anal.

Calcd. for $C_{21}H_{25}NO_3S$; C, 65.52; H, 5.92; N, 11.76; S, 6.73. Found: C, 65.43; H, 5.98 ; N, 11.63; S, 6.60.

EXAMPLE 71

N-(1-Adamantyl-5-(5-methyl-2-pyrazinylcarbonylamino)-2-naphthalenesulfonamide

Compound 71 was prepared using a procedure similar to Example 69. A mixture of the amine (Compound 66-2, 170 mg, 0.47 mmol), 5-methyl-2-pyrazinecarboxylic acid (116 mg, 0.62 mmol), BOP reagent (281 mg, 0.668 mmol) and DIEA (0.30 ml, 1.67 mmol) in THF (60 ml) was stirred for 18 h. Usual workup followed by purification by Chromatotron using hexane/EtOAc (4:1) as an eluent provided a white solid (64 mg, 28.1 %). ^{1}H NMR ($CDCl_3$): δ 1.53 (6H, br s, alkyl), 1.80 (6H, br s, alkyl), 1.96 (3H, br s, alkyl), 2.73 (3H, s, Me), 7.66 (1H, t, J = 7.5 Hz, ArH), 7.83 (1H, d, J= 8.4 Hz, ArH), 7.99 (1H, d, J = 7.5 Hz, ArH), 8.11 (1H, d, J= 9.0, ArH), 8.42 (1H, d, J = 6.9 Hz, ArH), 8.50 (2H, d, J = 4.5 Hz, ArH), 9.41 (1H, br s, ArH), 10.28 (1H, b s, -ArN<u>H</u>CO-).

EXAMPLE 72

2-(5-(2-Pyridylcarbonylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 72 was prepared using a procedure similar to that used in Example 68. A mixture of 0.13 g (0.38 mmol) of the amine (Compound 64-2), 0.52 g (0.42 mmol) of picolinic acid, 0.22 ml of DIEA and 0.16 g (0.39 mmol) of BOP afforded the crude material. Purification by Chromatotron using hexane/EtOAc (4:1) as an eluent gave a yellow solid, (55 mg, 31 %). ^{1}H NMR ($CDCl_3$): δ 1.41-1.49 (6H, m, alkyl), 1.68-1.90 (6H, m, alkyl), 2.19 (1H, br m, alkyl), 3.47 (2H, d, J = 3.6 Hz, CH_2N), 4.51 (1H, br m, -C<u>H</u>N-), 7.56 (1H, qd, $J_{1,2}$ =6.9, 0.9 Hz, ArH), 7.70 (1H, t, J = 7.5 Hz, ArH), 7.83 (1H, d, J = 9.0 Hz, ArH), 7.95 (2H, qd, $J_{1,2}$ = 12.1, 1.8 Hz, ArH), 8.19 (1H, d, J = 9.0 Hz, ArH), 8.36 (1H, d, J = 7.8 Hz, ArH), 8.43 (1H, d, J = 1.5 Hz, ArH), 8.50 (1H, d, J = 7.2 Hz,

ArH), 8.72 (1H, d, J = 4.5 Hz, ArH); ESMS (*m/z*) 462 (MH^+).

EXAMPLE 73

2-(5-(2-Furoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

2-Furoyl chloride (0.031 ml, 0.31 mmol) was added to a solution of the amine (Compound 64-2, 100 mg, 0.281 mmol) and DIEA (0.138 ml) in CH_2Cl_2 (75 ml). The solution was stirred for 18 h and concentrated. The concentrate was dissolved in EtOAc (100 ml) and extracted with 1N HCl (2 x 50 ml) and satd. Na_2CO_3 (2 x 50 ml). The organic layer was filtered though a 20 g silica plug and concentrated. Further purification was done by Chromatotron with hexane/EtOAc (4:1) as the eluent. The solution was then concentrated to give compound 73 as a white solid (0.12 g, 98 %). ^{1}H NMR (CD_3OD): δ 1.43-1.47 (6H, m, alkyl), 1.78-1.86 (6H, m, alkyl), 2.26 (1H, br s, alkyl), 3.44 (2H, d, J = 4.5 Hz, -CH_2N-), 4.45 (1H, br s, -N<u>H</u>C-), 6.57-6.59 (1H, m, ArH), 7.28 (1H, d, J = Hz, ArH), 7.59 (2H, t, J = 10.0 Hz, ArH), 7.77 (2H, d, J = 5.1, ArH), 8.04 (1H, d, J = 8.2, ArH), 8.08 (1H, d, J = 7.8, ArH), 8.33 (1H, d, J = 1.5, ArH), 8.68 (1H, br s, -N<u>H</u>CO); ESMS (*m/z*) 451 (M+H); Anal. calcd for $C_{25}H_{26}N_2O_4S$: C, 66.65; H, 5.82; N, 6.22; S, 7.12; found: C, 66.38; H, 5.83; N, 6.13; S, 7.03.

EXAMPLE 74

2-(5-(2-Nitrobenzoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 74 was prepared in a fashion similar to Example 73 from a mixture of the amine (Compound 64-2, 0.18g, 0.49 mmol), 0.078g (0.58 mmol) 2-nitrobenzoyl chloride and 0.25 ml DIEA in 40 ml of CH_2Cl_2. Purification by Chromatotron using hexane/EtOAc (4:1) followed by crystallization from hexane/EtOAc 4:1 gave yellow needles 0.19 g (75 %). mp 198.8-200.0 °C; ^{1}H NMR ($CDCl_3$): δ 1.43 (6H, m, alkyl), 1.86 (6H, m, alkyl), 2.23

(1H, m, alkyl), 3.37 (2H, d, J = 3.3 Hz, $-CH_2N-$), 4.35 (1H, br s, -C<u>H</u>N), 7.53-7.58 (3H, m, ArH), 7.70-7.77 (3H, m, ArH), 7.98 (2H, d, J = 9.0 Hz, ArH), 8.08 (1H, d J = 8.1, ArH), 8.20 (1H, s, ArH), 8.50 (1H, br s, -N<u>H</u>CO-); ESMS (*m/z*) 506 $(M+H^+)$; Anal. calcd for $C_{27}H_{27}N_3O_5S$; C, 64.14; H, 5.38; N, 8.31; S, 6.34; found: C, 64.27; H, 5.47; N, 8.22; S, 6.25.

EXAMPLE 75

2-(5-(2-Aminobenzoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A mixture of the nitro derivative (Compound 74, 74 mg, 0.15 mmol) and Pd/C (10%, ca. 100 mg) in 30 ml of EtOAc was hydrogenated at 70 psi. for 6 h. After usual workup followed by crystallization from hexane/EtOAc compound 75 was obtained as a white solid (38 mg, 54 %). ^1H NMR $(CDCl_3)$: δ 1.25-1.35 (6H, m, alkyl), 1.42-1.49 (6H, m, alkyl), 2.23 (1H, br m, CH), 3.49 (2H, d, J = 3.6 Hz, CH_2N), 4.48 (1H, br t, J = 4.8 Hz, CHN), 4.60 (2H, br s, $ArNH_2$), 6.78 (2H, t, J = 6.9 Hz, ArH), 7.31 (1H, td, J = 9.0, 0.9, ArH), 7.61 (1H, t, J =8.1 Hz, Ar), 7.67 (1H, d, J = 8.4 Hz, ArH), 7. 81 (2H, q, J = 8.4, 2 x ArH), 7.97 (1H, d, J = 7.5 Hz, ArH), 8.03 (1H, d, J = 9.0, ArH), 8.25 (1H, s, ArH), 8.67 (1H, d, J = 0.9 Hz, -ArN<u>H</u>CO-); ESMS (*m/z*) 474 (M - H).

EXAMPLE 76

2-(5-(3-Nitrobenzoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 76 was prepared using a procedure similar to that of Example 74. A mixture of the amine (compound 64-2, 0.13 g, 0.35 mmol), 0.72 g (0.39 mmol) of 3-nitrobenzoyl chloride and 0.36 ml of DIEA in 100 ml of THF was stirred for 16 h. Purification by Chromatotron using hexane/EtOAc (4:1) as an eluent, followed by crystallization from 5 ml hot hexane and a minimal amount of EtOAc gave 0.13 g of a white powder (70.9 %). ^1H NMR (CD_3OD): δ 1.25-1.48 (6H, m, alkyl), 1.76 (6H, m,

alkyl), 2.23 (1H, m, alkyl), 3.47 (2H, d, J = 3.6 Hz, -CH_2N-), 4.40 (1H, br s, -C<u>H</u>N-), 7.42 (1H, t, J = 7.8 Hz, ArH), 7.81-7.93 (3H, m, ArH), 8.17-8.25 (2H, m, ArH), 8.49-8.55 (3H, m, ArH), 8.94 (1H, s, ArH), 10.93 (1H, br s, -N<u>H</u>CO); ESMS (*m/z*) 523 ([M+NH_4]$^+$); Anal. calcd for $C_{27}H_{27}N_3O_5S$; C, 64.14; H, 5.38; N, 8.31, S, 6.34; found: C, 63.88; H, 5.47; N, 8.09; S, 6.11.

EXAMPLE 77

2-(5-Acetylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A mixture of the amine (compound 64-2, 0.035 g, 0.1 mmol), acetyl chloride (15 µl, 0.2 mmol) and DIEA (39 µl, 0.22 mmol) in CH_2Cl_2 (3 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 and the solution was washed with water, dried and stripped. The residue was purified by flash column chromatography using MeOH/CH_2Cl_2 (2%) to yield 20 mg of compound 77. ^{1}H NMR ($CDCl_3$): δ 1.25-1.60 (m, 6 H), 1.75-2.05 (m, 6 H), 2.21-2.40 (m, 4 H), 3.50 (m, 2 H), 4.23 (m, 1 H), 7.45 -7.55 (m, 1 H), 7.51-7.70 (m, 1 H), 7.70-7.80 (m, 1 H), 7.80-8.05 (m, 1 H), 8.05 -8.15 (m, 1H), 8.25 (m, 1 H).

EXAMPLE 78

2-(5-(4-*tert*-Butoxycarbonylaminobutyrylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 78 was prepared using a procedure similar to that of Example 68 from a mixture of the amine (compound 64-2, 0.55 g, 1.55 mmol), 0.79 g (3.82 mmol) 4-*tert*-butoxycarbonylaminobutyric acid, 1.51 ml of DIEA and 1.70 g (4.02 mmol) of BOP reagent. Purification by Chromatotron using hexane/EtOAc (4:1) gave a tan solid, 0.13 g (15 %); ^{1}H NMR ($CDCl_3$): δ 1.45-1.48 (15H, br m, aklyl), 1.79-1.93 (8H, br m, aklyl), 2.23 (1H, t, alkyl), 2.57 (1H, t, aklyl), 3.30 (1H, q, aklyl), 3.47 (2H, q, -CH_2N-), 4.47 (1H, t -C<u>H</u>N-), 4.93 (1H, br t, aklyl), 7.58 (1H, t, J = 7.8 Hz, ArH), 7.75 (1H, br s,

ArH), 7.78 (1H, d, J = 3.0 Hz, ArH), 8.13 (1H, d J = 7.2, ArH), 8.28 (1H, s, J = 9.0, ArH), 8.34 (1H, s, ArH), 9.32 (1H, br s, CONH); ESMS (*m/z*) 559 ($[M+NH_4]^+$)

EXAMPLE 79

2-(5-(4-Aminobutyrylamino-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 79 was prepared by stirring a mixture of the N-Boc-amine (compound 78, 0.12 g, 0.23 mmol) in 15 ml of CH_2Cl_2 and 15 ml of TFA at room temperature for 1 h. The solution was concentrated, then redissolved in 60 ml of CH_2Cl_2 and extracted with 2 x 20 ml of satd. Na_2CO_3. The organic layer was filtered through a 20 g silica plug and concentrated. Further purification by Chromatotron using CH_2Cl_2/MeOH (5:1) afforded a yellow solid (0.91 g, 92 %). ^{1}H NMR ($CDCl_3$): δ 1.45 (6H, br s, alkyl), 1.82-2.17 (8H, br m, $-CH_2-$), 1.86-2.17 (6H, br m, alkyl), 2.23 (1H, t, J = 8.1 Hz, alkyl), 2.76 (1H, t, J = 6.3 Hz, aklyl), 3.07 (1H, q, J = 5.4, -C$\underline{H}$N-), 3.30 (2H, q, J = 6.6 Hz, $-CH_2N-$), 3.50 (1H, d, J = 3.6 Hz, aklyl), 4.56 (1H, t, J = 1.2 Hz, -C$\underline{H}$N-), 4.84 (2H, br s, $-NH_2$), 7.62 (1H, t, J = 7.8 Hz, ArH), 7.78 (1H, dd, J = 7.2, ArH), 7.78 (1H, dd, J = 9.0, 1.8 Hz, ArH), 7.97 (1H, t J = 8.1, ArH), 8.20 (1H, s, J = 9.0, ArH), 8.44 (1H, br s, ArH).

EXAMPLE 80

2-(5-(1-*tert*-Butoxycarbonyl-2-piperidylcarbonylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

t-Butylacetyl chloride (0.035 ml, 0.45 mmol) was added to a solution of the N-Boc-pipecolinic acid (0.13 g, 0.45 mmol) and DIEA (0.20 ml, 1.22 mmol) in THF (30 ml) at 0 °C and the mixture was stirred for 1 h. A solution of the amine (compound 64-2, 0.17 g, 0.41 mmol) in THF (5 ml) was added and the reaction mixture was stirred for an additional 18 h and concentrated. The residue was taken up in 50 ml of EtOAc and extracted successively with 2 x 50 ml of 1N HCl and 2 x 50 ml of

satd. Na_2CO_3. The organic layer was filtered through 20 g silica and concentrated. Further purification by Chromatotron using hexane/EtOAc (4:1) afforded compound 80 as a tan foam (72 mg, 31.4 %). ^1H NMR ($CDCl_3$): δ 1.05 (2H, br s, alkyl), 1.35 (8H, br s, alkyl), 1.48 (15H, br s, alkyl), 1.70-1.82 (4H, br m, alkyl), 2.19 (1H, br s, -CH-), 2.50 (1H, t, J = 7.2 Hz, alkyl), 3.05 (1H, q, J = 5.7 Hz, alkyl), 3.47 (1H, br s, alkyl), 4.4 (1H, br s, -C<u>H</u>N-), 7.55 (1H, t, 7.5 Hz, ArH), 7.66-7.76 (2H, br m, ArH), 7.90 (1H, d, J = 7.5 Hz, ArH), 7.98 (1H, d, J = 7.5 Hz, ArH), 8.20 (1H, d, ArH), 8.26 (1H, br s, -NHCO-); ESMS (*m/z*) 538 ($M-2Cl^-$).

EXAMPLE 81

2-(5-(2-Piperidylcarbonylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 81 was prepared by stirring a mixture of the N-Boc-amine (compound 80, 0.052 g, 0.093 mmol) in 15 ml of CH_2Cl_2 and 15 ml of TFA at room temperature for 1h. Purification by Chromatotron using CH_3CN/H_2O (5:1) as the eluent afforded a tan solid (26.4 mg, 60.4 %): ^1H NMR ($CDCl_3$): δ 1.31-1.58 (12H, m, alkyl), 1.79-1.82 (4H, br m, alkyl), 1.93 (2H, s, alkyl), 2.27 (1H, br s, -CH-), 2.59 (1H, t, J = 7.6 Hz), 2.87 (1H, t, J = 7.2 Hz, alkyl), 3.31 (2H, d, J 1.8 Hz, -NC<u>H</u>$_2$-), 3.52 (1H, d, J = 2.3 Hz), 7.65 (1H, d , J = 11.4 Hz, ArH), 7.74 (2H, d, J = 7.5 Hz, 2 x ArH), 7.86 (1H, dd, J = 8.7, 2.1, ArH) 7.92 (1H, br d, J = 8.1 Hz, ArH), 8.14 (1H, d, J = 9.0 Hz, ArH), 8.44 (1H, d, 1.50, -NHCO-).

EXAMPLE 82

5-(5-(*tert*-Butoxycarbonylaminoacetylamino)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

DIEA (0.14 ml, 0.8 mmol) was added to an ice-cold solution of N-Boc-glycine (0.064 g, 0.4 mmol) in THF (4 ml) followed by a solution of t-butylacetyl chloride (55 μl, 0.4 mmol) in THF (1 ml). The reaction mixture was stirred for 45 min at 0 °C. A solution of the amine

(compound 65-2, 117 mg, 0.365 mmol) in THF (3 ml) was added followed by DMAP (0.05 g, 0.4 mmol) and the resulting mixture was stirred at room temperature for 18 h. The THF was distilled away, and the residue partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried and stripped. The residue was chromatographed to give compound 82 (90 mg); ESMS : m/z 478 (MH^+).

EXAMPLE 83

5-(5-Aminoacetylamino)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

A solution of the above Boc amine (compound 82, 0.095 g, 0.2 mmol) in a mixture of CH_2Cl_2 (10 ml) and TFA (7.5 ml) was stirred at room temperature for 7 h. After usual workup the crude material was purified by flash chromatography (2-5% MeOH/$CHCl_3$) to give 0.05 g of compound 83. ^1H NMR ($CDCl_3$): δ 1.60 - 2.05 (m, 4 H), 2.90 -3.05 (m, 1 H), 3.10-3.20 (m, 1 H), 3.50 (s, 2 H), 3.75 (m, 3 H), 4.65 (s, 1 H), 7.60 (m, 1 H), 7.75 (m, 1 H), 8.05 (d, 2 H), 8.25 -8.55 (m, 2 H), 10.12 (br s, 1 H). ESMS : m/z 378 (MH^+).

EXAMPLE 84

2-(5-(4-Methoxycarbonylbenzoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 84 was prepared from 0.22 g (0.62 mmol) of the amine (compound 64-2), monomethylterephthalate (0.15 g, 0.83 mmol), 0.35 ml of DIEA and 0.36 g (0.86 mmol) of BOP reagent. Purification by Chromatotron using hexane/EtOAc (4:1) as an eluent gave a white solid, 0.265 g (82.7 %): ^1H NMR ($CDCl_3$): δ 1.47-1.49 (6H, m, alkyl), 1.76-1.87 (6H, m, alkyl), 2.25 (1H, br s, CH), 3.50 (2H, br s, CH_2N), 4.00 (3H, s, Me), 4.51 (1H, br s, C$\underline{H}$N), 7.39 (1H, t, J = 3.3 Hz, ArH), 7.45-7.50 (2H, m, 2 x ArH), 7.58 (1H, t, J = 8.1 Hz, ArH), 7.73 (1H, dd, J = 7.8,1.58, 2 x ArH), 7.10 (1H, d, J = 8.7 Hz, ArH), 8.11 (1H, d, J = 7.8, ArH), 8.25 (2H, d,

J = 12 Hz, ArH), 8.35 (2H, d, J = 6 Hz, ArH); ESMS (*m/z*) 317 ([M-H]$^+$).

EXAMPLE 85

2-(5-(4-Carboxybenzoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

To a solution of the above methyl ester (compound 84, 150 mg, 0.289 mmol) in 50 ml of THF was added a solution of LiOH (17 mg, 0.723 mmol) in water (3 ml). MeOH (5 ml) was added until the solution was clear. The reaction was stirred for 18 h and concentrated. The concentrate was taken up in EtOAc (75 ml) then extracted with 1N HCl (2 x 50 ml). The organic layer was filtered through 20 g of silica and concentrated. The residue was crystallized from MeOH/CH_2Cl_2 to provide compound 85 as a tan solid (134 mg, 94.6%). ^{1}H NMR (CD_3OD): δ 1.39-1.51 (6H, m, alkyl), 1.81-1.94 (6H, m, alkyl), 2.46 (1H, br m, CH), 3.50 (2H, d, J = 3.9 Hz, CH_2N), 4.48 (1H, br m, -CHN-), 7.71 (1H, t, J = 9.0, ArH), 7.80 (1H, d, J = 7.50, 2 x ArH), 7.90 (1H, dd, J = 9.0, 1.8 Hz, ArH), 8.06 (1H, d, J = 8.4 Hz, ArH), 8.07 (1H, s, -N<u>H</u>CO-), 8.14-8.21 (5H, m, 5 x Ar), 8.46 (1H, d, J = 1.8 Hz, ArH); ESMS (*m/z*) 503 (MH$^-$);

EXAMPLE 86

2-(5-(6-Methylnicotinoylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 86 was prepared using a procedure similar to that of Example 68. A mixture of 0.066 g (0.188 mmol) of the amine (compound 64-2), 0.035 g (0.207 mmol) of 6-methylnicotinic acid, 0.062 ml (0.376 mmol) of DIEA and 0.075 g (0.294 mmol) of BOP-Cl afforded the crude material. Purification by Chromatotron using hexane/ EtOAc (4/1) as an eluent gave a yellow solid, (65 mg, 73 %). ESMS (*m/z*) 476 (MH$^+$).

EXAMPLE 87

2-(4-(2-(Pyrazinylaminocarbonyl)-5-naphthalenesulfonyl)-2-azatricyclo[4.3.1.$1^{4,8}$]undecane

Compound 87 was prepared using a procedure similar to that of Example 69. A mixture of the carboxylic acid (compound 118), (0.050g, 0.129 mmol), 2-aminopyrazine (16 mg, 0.167 mmol), BOP reagent (76.2 mg, 0.180 mmol) and DIEA (0.739 ml, 0.452 mmol) in THF (30 ml) was stirred for 18 h. Usual workup followed by purification by Chromatotron using hexane/EtOAc (4:1) as an eluent provided the compound 87. ESMS *m/z* 462 (MH^+).

EXAMPLE 88

5-(5-Chloroacetylamino-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Chloroacetyl chloride (1 mmol, 80 μl) was added to a solution of the amine (Compound 65-2, 0.32 g, 1 mmol) and DIEA (1.1 mmol, 190 μl) in CH_2Cl_2 (5 ml) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 (15 ml) and the solution was washed with water, dried over anhydrous $MgSO_4$ and stripped. The residue was dried under high vacuum to yield the chloroacetyl derivative (compound 88) as a tan foam. ^{1}H NMR ($CDCl_3$): δ 1.40 - 1.68 (m, 2 H), 2.90 (dd, 1 H), 3.12 (d, 1 H), 3.28 - 3.50 (m, 2 H), 3.57 (d, 1 H), 4.22 (s, 2 H), 4.60 (s, 1 H), 7.60 (t, 1 H), 7.58 - 7.85 (m, 2 H), 7.88 - 8.05 (m, 2 H), 8.32 (s, 1 H), 8.65 (br s, 1 H). This material was used as is in any additional reactions.

EXAMPLE 89

2-(5-Chloroacetylamino-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.$1^{4,8}$]undecane

Compound 89 was prepared as described in Example 88 from the amine (compound 64-2). ESMS :*m/z* 434 (MH^+).

EXAMPLE 90

N-(1-Adamantyl)-5-chloroacetylamino)-2-naphthalenesulfonamide

Compound 90 was prepared as described in Example 88 from the amine (compound 66-2). ESMS :*m/z* 433 (MH^+).

EXAMPLE 91

5-(5-(N,N-dimethylaminoacetylamino)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

A solution of the chloride (compound 88, 0.05 g, 0.125 mmol), dimethylamine hydrochloride (0.033 g, 0.375 mmol) and DIEA (0.8 mmol, 0.13 ml) in CH_2Cl_2 (5 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (15 ml) and the solution washed with water, dried over anhydrous $MgSO_4$ and stripped. The residue was purified by flash chromatography ($MeOH/CH_2Cl_2$ 1%) to yield 31 mg of compound 91. ^1H NMR ($CDCl_3$): δ 1.60 - 1.85 (m, 2 H), 2.32 (s, 6 H), 2.90 -3.05 (m, 1 H), 3.10-3.20 (m, 1 H), 3.25 (s, 2 H), 3.50 - 3.75 (m, 3 H), 4.32 (s, 1 H), 7.60 (m, 1 H), 7.75 (d, 1 H), 7.88 - 8.05 (m, 2 H), 8.32 (s, 1 H), 8.40-8.60 (m, 1 H), 8.85 (br s, 1 H). mp. 108-110 °C

EXAMPLE 92

5-(5-(4-Hydroxypiperidinoacetylamino)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 92 (40 mg) was synthesized as in Example 91 from the chloride (compound 88, 0.05 g, 0.125 mmol), 4-hydroxypiperidine (0.014 g, 0.14 mmol) and DIEA (40 μl, 0.22 mmol). ^1H NMR ($CDCl_3$): δ 1.40 - 1.85 (m, 6 H), 1.85-2.12 (m, 2 H), 2.40-2.65 (m, 2 H), 2.80-3.12 (m, 3 H), 3.25 (s, 2 H), 3.40 - 4.0 (m, 4 H), 4.32 (s, 1 H), 7.60 (m, 1 H), 7.75 (d, 1 H), 7.88 - 8.05 (m, 2 H), 8.25 -8.50 (m, 2 H), 9.85 (br s, 1 H). ESMS :*m/z* 462 (MH^+). mp. 115-120 °C

EXAMPLE 93

5-(5-Morpholinoacetylamino-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 93 (30 mg) was synthesized as in Example 91 from the chloride (compound 88, 0.05 g, 0.125 mmol), morpholine (0.011 g, 0.13 mmol) and DIEA (40 μl, 0.22 mmol). ^{1}H NMR ($CDCl_3$): δ 1.10-1.40 (m, 1 H), 1.60-1.85 (m, 1 H), 2.65 (s, 4 H), 2.80-3.02 (m, 1 H), 3.02-3.12 (m, 1 H), 3.30 (s, 2 H), 3.40 - 3.70 (m, 3 H), 3.85 (s, 4 H), 4.32 (s, 1 H), 7.50-7.70 (m, 1 H), 7.80-7.90 (m, 2 H), 7.88 - 8.05 (m, 2 H), 9.85 (br s, 1 H).

EXAMPLE 94

5-(5-(4-Methyl-1-piperazinyl)acetylamino-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Compound 94 (25 mg) was synthesized as in Example 91 from the chloride (compound 88, 0.05 g, 0.125 mmol), N-methylpiperazine (0.013 g, 0.14 mmol) and DIEA (40 μl, 0.22 mmol). ^{1}H NMR ($CDCl_3$): δ 1.10-1.25 (m, 1 H), 1.60-1.85 (m, 1 H), 2.35 (s, 3 H), 2.45-2.70 (m, 4 H), 2.70-2.80 (m, 4 H), 2.80-3.02 (m, 1 H), 3.02-3.12 (m, 1 H), 3.25 (s, 2 H), 3.30 - 3.55 (m, 2 H), 3.55 -3.70 (m, 1 H), 4.63 (s, 1 H), 7.50-7.70 (m, 1 H), 7.70-7.90 (m, 1 H), 7.80 - 8.05 (m, 2 H), 8.25-8.45 (m, 2 H), 9.85 (br s, 1 H).

EXAMPLE 95

N-(1-Adamantyl)-5-(N,N-dimethylaminoacetylamino)-2-naphthalenesulfonamide

Compound 95 (15 mg) was prepared as in Example 91 from the chloride (compound 90, 0.02 g, 0.046 mmol), dimethylamine hydrochloride (0.02 g, 0.23 mmol), KI (10 mg) and DIEA (60 μl, 0.35 mmol) in THF (2.5 ml). ^{1}H NMR ($CDCl_3$): δ 1.50-1.85 (m, 7 H), 1.60 (s, 6 H), 2.98 (dd, 1 H), 3.10 (dd, 1 H), 3.40-3.51 (m, 3 H), 3.60 (dd, 1 H), 4.05 (dd, 2 H), 4.65 (s, 1 H), 5.40 (br s, 1 H), 7.60 (m, 1 H), 7.75-7.85 (m, 2 H), 8.05-8.25 (m, 2 H), 8.35 (br s, 1 H), 8.45 (s, 1 H), 9.00 (br s, 1 H). ESMS :m/z 442 (MH+). mp. 188 °C.

EXAMPLE 96

5-(5-(3-Benzoylthioureido)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

Benzoyl chloride (29 μl, 0.25 mmol) was added to a hot solution of NH_4NCS (0.02 g, 0.25 mmol) in acetone (2 ml) and the reaction mixture refluxed for 0.5 h. A solution of the amine (compound 65-2, 0.8 g, 0.25 mmol) in CH_3CN (4 ml) was added and the mixture refluxed for 4 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water, dried and stripped. The residue was flash chromatographed ($MeOH/CH_2Cl_2$, 1%) to yield 90 mg of compound 96. ^1H NMR ($CDCl_3$): δ 1.60 - 1.85 (m, 2 H), 2.90 -3.05 (m, 1 H), 3.10-3.20 (m, 1 H), 3.50 - 3.75 (m, 3 H), 4.32 (s, 2 H), 7.60 (d, 2 H), 7.65 -7.75 (m, 2 H), 7.80 - 8.15 (m, 4 H), 8.15 (s, 2 H), 8.23 (s, 1 H), 9.35 (s, 1 H). ESMS :*m/z* 484 (MH^+).

EXAMPLE 97

N-(1-Adamantyl)-5-(3-benzoylthioureido)-2-naphthalenesulfonamide

Compound 97 (20 mg) was synthesized as in Example 96 from the amine (compound 66-2, 0.089 g , 0.25 mmol) and benzoylisothiocyanate (0.04 g, 0.25 mmol prepared from benzoyl chloride and NH_4NCS in acetone). ^1H NMR ($CDCl_3$): δ 1.25-2.20 (m, 15 H), 7.00 - 8.05 (m, 12 H), 8.15 (s, 2 H), 9.05 (s, 1 H), 10.05 (s, 1 H).

EXAMPLE 98

5-(5-Thioureido-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

NaOH (10%, 0.16 ml) was added to a suspension of the benzoylurea (compound 96, 90 mg) in EtOH (2.5 ml) and the solution was heated under reflux for 2 h. The reaction mixture was stripped, the residue was diluted with water and the solution extracted with CH_2Cl_2. The organic layer was dried, stripped and the residue was

purified by flash chromatography ($MeOH/CH_2Cl_2$, 2%) to yield 30 mg of compound 98 as a yellow solid. ^1H NMR ($CDCl_3$): δ 1.60 - 1.85 (m, 3 H), 2.90 -3.05 (m, 1 H), 3.10-3.20 (m, 1 H), 3.50 - 3.75 (m, 3 H), 4.32 (s, 1 H), 6.0 (br 1 H), 7.60 (m, 2 H), 7.75 -7.95 (m, 2 H), 8.15 (s, 1 H), 8.35 (s, 1 H), 9.35 (s, 1 H). ESMS :*m/z* 380 (MH^+).

EXAMPLE 99

5-(5-(3-(2-Thiazolyl)thioureido)-2-naphthalenesulfonyl)-5-aza-2-thiabicyclo[2.2.1]heptane

A solution of 1,1'-thiocarbonyldiimidazole (2.22 g, 12.5 mmol) and 2-aminothiazole (1.25 g, 12.5 mmol) in CH_3CN was refluxed for 2 h. The reaction mixture was cooled, filtered, and the residue was washed with cold CH_3CN and air-dried to give 1.4 g of the thioamide intermediate 99c. A mixture of the thioamide 99c (0.035 g, 0.16 mmol) and the amine (compound 65-2, 0.053 g, 0.15 mmol) in CH_3CN (3 ml) was heated under reflux for 3 h. The solution was evaporated and the residue was flash chromatographed ($MeOH/CH_2Cl_2$; 2-4%) to give 0.03 g of the compound 99 as a light yellow solid. ^1H NMR ($CDCl_3$): δ 1.30 (d, 1 H), 1.55 (d, 1 H), 2.90 -3.05 (m, 2 H), 3.30-3.50 (m, 2 H), 3.55 (s, 1 H), 4.75 (s, 1 H), 7.00-7.10 (m, 1 H), 7.35-7.55 (m, 1 H), 7.65 -7.95 (m, 3H), 8.05-8.20 (m, 2 H), 8.55 (s, 1 H). ESMS :*m/z* 463 (MH^+).

EXAMPLE 100

2-(5-(3-(2-Thiazolyl)thioureido)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 100 was prepared in a fashion analogous to Example 99 from the above thioamide intermediate 99c and the amine (compound 64-2). ^1H NMR ($CDCl_3$): δ 1.06-1.25 (m, 4 H), 1.25-1.55 (m, 4 H), 1.55-2.05 (m, 4 H), 2.13 (br m, 1 H), 3.48 (s, 2 H), 4.17 (s, 1 H), 6.80 (s, 1 H), 7.15-7.48 (m, 2 H), 7.48-8.12 (m, 7 H), 8.30 (s, 1 H);

ESMS :m/z 499 (MH^+).

EXAMPLE 101

2-(5-(2-Pyridylmethylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A solution of the amine (compound 64-2, 100 mg, 280 mmol), 2-pyridinecarbaldehyde (33 ml, 0.393 mmol), and sodium cyanoborohydride (63 mg, 0.98 mmol) in MeOH (50 ml) and acetic acid (0.5 ml) was stirred at room temperature for 18 hr. The solvent was evaporated and the residue was partitioned between EtOAc and sat'd. aqueous Na_2CO_3. The EtOAc layer was washed with H_2O, dried (Na_2SO_4) and concentrated and the residue was passed through a plug of silica (EtOAc). The filtrate was concentrated and the residue was purified by Chromatotron (hexane/EtOAc, 4:1) to provide the compound 101 as a white foam (84 mg, 63.3%): ^1H NMR ($CDCl_3$): δ 1.36-1.51 (6H, m, alkyl), 1.82-2.00 (6H, m, alkyl), 2.23 (1H, br m, -CH-), 3.30 (1H, t, J = 1.5 Hz, -C$\underline{H}$N-), 4.50 (1H, br s, -NC$\underline{H}_2$-), 4.69 (2H, br s, -NHC$\underline{H}_2$Ar), 5.97 (1H, br s, --N$\underline{H}$Ar), 6.69 (1H, d, J = 7.5 Hz, ArH), 7.20-7.25 (1H, m, ArH), 7.30-7.46 (3H, m, ArH), 7.67 (1H, dd, J = 14, 1.8 Hz, ArH), 7.77 (1H, dd, J = 14, 1.8 Hz, ArH), 8.10 (1H, d, J = 9.0 Hz, ArH), 8.30 (1H, d, 1.8 Hz, ArH), 8.63 (1H, d, J = 3.0 Hz, ArH); Anal.calcd for $C_{26}H_{29}N_3O_2S$: C, 69.77; H, 6.53; N, 9.39; S, 7.16. Found: C, 69.52; H, 6.53; N, 9.33; S, 7.18. ESMS (m/z) ($M + H^+$) 448.

EXAMPLE 102

2-(5-(2,4-Dinitrophenylamino)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

CH_3Li (0.24 ml, 0.806 mmol) was added to a solution of the amine (compound 64-2, 0.25 g, 0.70 mmol, 9039) in 25 ml of THF at -78 °C under N_2 atmosphere. 2,4-dinitroflorobenzene (0.097ml, 0.82 mmol) was added to the above mixture and the resultant mixture was stirred at room temperature for 18 h. The solution was then

concentrated, and the residue was partitioned between 75 ml of EtOAc and saturated aqueous Na_2CO_3 (50 ml). The organic layer was separated and filtered through a silica plug (20 g) and stripped. Further purification by Chromatotron using hexane/EtOAc (4:1) followed by crystallization from CH_2Cl_2/EtOAc gave compound 102 as orange crystals (263 mg, 71.7%): ^{1}H NMR ($CDCl_3$): δ 1.45-1.52 (6H, m, alkyl), 1.82-2.00 (6H, m, alkyl), 2.26 (1H, br s, -CH-), 3.49 (2H, q, J = 5.7 Hz, -CH_2N-), 4.50 (1H, t, J = 4.5 Hz, -C<u>H</u>N-), 6.83 (1H, d, J = 9.6 Hz, ArH), 7.69 (2H, m, 2 x ArH), 7.86 (1H, dd, J = 7.2, 1.5, ArH), 8.01-8.14 (3H, m, 3 x ArH), 8.49 (1H, d, J = 1.5, ArH), 9.43 (1H, d, J = 2.7 Hz, ArH), 10.19 (1H, br s, ArN<u>H</u>Ar); Anal.calcd for $C_{26}H_{26}N_4O_6S$: C, 59.58; H, 5.01; N, 10.72; S, 6.13. Found: C, 59.58; H, 5.06; N, 10.44; S, 5.95. ESMS 523 (*m/z*) (M + H$^+$).

EXAMPLE 103

2-(4-(2,4-Dinitrophenyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Sodium hydride (16 mg, 402 mmol, 60% dispersion in oil) was added to a solution of compound 54 (100 mg, 279 mmol) in DMF (35 ml). Then 4-fluoro-1,3-dinitrobenzene (0.04 ml, 364 mmol) was added and the mixture was stirred at room temperature for 18 h. At this time the solvent was evaporated and the residue was partitioned between EtOAc and 1N HCl. The organic phase was washed with satd. aqueous Na_2CO_3, dried (Na_2SO_4) and concentrated. The residue was filtered through a plug of silica (EtOAc) and the filtrate was concentrated to provide a yellow solid (190 mg). This material was further purified by Chromatotron (30% EtOAc/hexane and the product was crystallized from EtOAc and hexane to provide compound 103 as yellow crystals (116 mg, 79%): ^{1}H NMR ($CDCl_3$): δ 1.41-1.59 (6H, m, alkyl), 1.80-2.02 (6H, m, alkyl), 2.27 (1H, br m, CH), 3.48 (2H, d, J = 3.6 Hz, CH_2N), 4.44 (1H, br t, J = 4.5 Hz, CHN), 6.97 (1H, d, J = 9.3 Hz, ArH), 7.51 (1H, d, J = 0.9 Hz, ArH),

7.68-7.79 (2H, m, 2 x ArH), 8.05-8.15 (2H, m, 2 x ArH), 8.30 (1H, dd, J = 9.0, 2.4 Hz, ArH), 8.36 (1H, s, ArH), 8.92 (1H, d, J = 3.0 Hz, ArH); Anal. calcd for $C_{26}H_{25}N_3O_7S$: C, 59.6; H, 4.8; N, 8.0; S, 6.1; found: C, 59.7: H, 4.8; N, 7.9; S, 6.1.

EXAMPLE 104

2-(4-(4-Nitrophenyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 104 was prepared in a manner similar to Example 103 starting from compound 54 (100 mg, 279 mmol), sodium hydride (14 mg, 352 mmol, a 60% dispersion in oil) and 4-fluoronitrobenzene (0.04 ml, 392 mmol) in DMF (35 ml). The crude material was purified by Chromatotron (CH_2Cl_2/EtOAc/MeOH, 3:0.9:0.1) and the product was triturated with Et_2O to provide a yellow powder (121 mg, 90.4 %): ^1H NMR ($CDCl_3$): δ 1.41-1.58 (6H, m, alkyl), 1.79-2.03 (6H, m, alkyl), 2.26 (br, m, CH), 3.47 (2H, d, J = 3.6 Hz, CH_2N), 4.45 (1H, br t, J = 4.5 Hz, CHN), 7.07-7.16 (2H, m, 2 x ArH), 7.46 (1H, d, J = 1.5 Hz, ArH), 7.64-7.78 (2H, m, 2 x ArH), 8.02-8.16 (2H, m, 2 x ArH), 8.20-8.36 (3H, m, 3 x ArH); ESMS (*m/z*) 479 ($M+H^+$).

EXAMPLE 105

3-(5-(4-Nitrophenyloxy)-2-naphthalenesulfonyl)-3-azabicyclo[3.2.2]nonane

Compound 105 was prepared using a procedure similar to that of Example 104. NaH (60 % dispersion in mineral oil, 0.028 g, 0.43 mmol) was added to a solution of compound 49 (0.10 g, 0.30 mmol) in 30 ml of anhydrous DMF and stirred for 20 min. Next 0.056 ml (0.39 mmol) of 4-nitrofluorobenzene was added to the mixture and stirred for 18 h. The reaction mixture was concentrated and purified by Chromatotron using (hexane/CH_2Cl_2/EtOAc, 6.5:3.0:0.05). The residue was triturated with hexane to provide a yellow powder (125 mg, 91.7 %). ^1H NMR ($CDCl_3$): δ 1.69 (8H, q, J = 2.3 Hz, $-CH_2-$), 2.09 (2H, br

s, -CH-), 3.47 (4H, d, J = 4.2 Hz, $-CH_2N-$), 7.08 (2H, d, J = 9.0 Hz, 2 x ArH), 7.30 (1H, dd, J = 6.6,0.9, ArH), 7.63 (1H, t, J = 8.1 Hz, ArH), 7.77 (1H, dd, J = 7.2,1.8, ArH), 7.89 (1H, d, J = 8.4, ArH), 8.14 (1H, d, J = 9.0, ArH), 8.22 (2H, d, J = 3.3, ArH), 8.41 (1H, d, J = 1.5, ArH); ESMS (*m/z*) 453 ($M+H^+$); Anal. calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19; S, 7.08; found: C, 63.61; H, 5.40; N, 6.16; S, 6.99.

EXAMPLE 106

2-(4-(4-Methyl-2-nitrophenyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 106 was prepared using a procedure similar used to preprare Example 104. Compound 54 (100 mg, 0.279 mmol), and sodium hydride (18 mg, 0.62 mmol, 60% dispersion in oil) were combined in DMF (35 ml). Then 4-fluoro-3-nitrotoluene (0.051 ml, 0.364 mmol) was added and the mixture was stirred at room temperature for 18 hr. At this time the solvent was evaporated and the residue was taken up in ethanol and filtered through a plug of silica. This material was further purified by Chromatotron (hexane/EtOAc, 7:3 as an eluent) to give a yellow solid (131 mg, 85.6%): ^1H NMR ($CDCl_3$): δ 1.41-1.50 (6H, m, alkyl), 1.79-2.03 (6H, m, alkyl), 2.26 (1H, br s, -CH-), 2.48 (3H, s, Me), 3.45 (2H, q, J = 3.9 Hz, $-CH_2N-$), 4.35 (1H, br t, J = 4.8 Hz, CHN), 7.03-7.05 (2H, d, ArH), 7.39 (1H, d, J = 8.4 Hz, ArH), 7.65-7.70 (2H, m, ArH), 7.87 (1H, br s, ArH), 7.97-8.01 (1H, m, ArH), 8.15 (1H, s, ArH), 8.32-8.35 (1H, m, ArH); ESMS (*m/z*) 493 ($M+H^+$).

EXAMPLE 107

2-(4-(5-Methyl-2-nitrophenyloxy)-2-naphthalenesulfonyl-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 107 was prepared in a similar fashion as described in Example 106 from a mixture of compound 54 (0.10 g, 0.30 mmol), NaH (60 % dispersion in mineral oil, 0.016 g , 0.37 mmol) and 3-fluoro-4-nitrotoluene

(0.054 g, 0.35 mmol). Purification by Chromatotron using hexane/EtOAc (4:1) as an eluent, followed by crystallization from EtOAc/hexane provided white crystals (98.6 mg, 75.2 %). mp 164.2-165.3 °C; ^{1}H NMR ($CDCl_3$): δ 1.41-1.51 (6H, m, aklyl), 1.75-1.92 (6H, m, aklyl), 2.23 (1H, br s, -CH-), 3.39 (3H, s, Me), 3.41 (2H, d, J = 3.6, -CH_2N-), 4.38 (1H, t, J = 5.1 Hz, -CHN-), 6.90 (1H, s, ArH), 7.11 (1H, d, J = 1.2, ArH), 7.15 (1H, d, J = 8.1, ArH), 7.68-7.72 (2H, m, ArH), 8.02 (2H, d, J = 8.7, ArH), 8.20 (1H, s, ArH), 8.31-8.34 (1H, m, ArH); ESMS (*m/z*) 493 (M+H$^+$); Anal. calcd. for $C_{27}H_{28}N_2O_5S$; C, 65.84; H, 5.73; N, 5.69; S, 6.51; found: C, 65.94; H, 5.79; N, 5.62; S, 6.41.

EXAMPLE 108

2-(4-(2-Nitro-4-trifluoromethylphenyloxy)-2-naphthalenesulfonyl-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 108 was prepared using a procedure similar to that of Example 107. A mixture of compound 54 (100 mg, 0.279 mmol), sodium hydride (18 mg, 0.62 mmol, a 60% dispersion in oil) and 4-fluoro-3-nitrobenzotrifluoride (0.051 ml, 0.364 mmol) in DMF (35 ml) was stirred at room temperature for 18 h. Purification by Chromatotron (hexane/EtOAc, 7:3 as an eluent) gave a yellow solid (131 mg, 85.6%): ^{1}H NMR ($CDCl_3$): δ 1.41-1.50 (6H, m, alkyl), 1.79-2.00 (6H, m, alkyl), 2.26 (1H, br s, -CH-), 3.45 (2H, q, J = 3.9 Hz, -CH_2N-), 4.43 (1H, t, J = 4.5 Hz, -CHN-), 7.03 (1H, d, J = 8.7 Hz, ArH), 7.38 (1H, d, J = 1.5 Hz, ArH), 7.69-7.75 (3H, m, ArH), 8.06 (1H, t, J = 3.6 Hz, ArH), 8.16 (1H, m, J = 4.5, ArH), 8.31 (2H, d, J = 3.9 Hz, ArH); ESMS (*m/z*) 547 (M+H).

EXAMPLE 109

2-(4-(4-Aminophenyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A mixture of the nitro compound 104 (95 mg, 0.198 mmol) in EtOAc (100 ml) and 10% Pd/C (ca. 100 mg) was

shaken under an atmosphere of hydrogen (75 psi) for 18 h. The mixture was filtered through a bed of Celite and the filtrate was concentrated. The residue was crystallized from EtOAc/hexane to provide compound 109 as tan needles (82.1 mg, 92.4 %): ^{1}H NMR ($CDCl_3$): δ 1.32-1.57 (6H, m, alkyl), 1.68-1.97 (6H, m, alkyl), 2.19 (1H, br m, CH), 3.37 (2H, d, J = 3.6 Hz, CH_2N), 3.68 (2H, br s, NH_2), 4.35 (1H, br t, J = 4.5 Hz, CHN), 6.62-6.83 (2H, m, 2 x ArH), 6.89-7.02 (3H, m, 3 x ArH), 7.59-7.72 (2H, m, 2 x ArH), 7.94 (1H, m, ArH), 8.04 (1H, s, ArH), 8.41 (1H, m, ArH); ESMS (*m/z*) 449 ($M+H^+$).

EXAMPLE 110

2-(4-(2,4-Diaminophenyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A mixture of the dinitrophenyl compound in Example 103 (131 mg, 0.244 mmol) in EtOAc (100 ml) containing (10% Pd/C, ca. 100 mg) was shaken under an atmosphere of hydrogen (75 psi) for 18 h. Usual workup and purification by Chromatotron (hexane/EtOAc, 2:1 as an eluent) gave a solid which upon trituration with hexane provided compound 110 as a tan solid (91.9 mg, 88.4%). mp 300 °C dec.; ^{1}H NMR ($CDCl_3$): δ 1.38-1.52 (6H, m, alkyl), 1.69-1.92 (6H, m, alkyl), 2.18 (1H, br m, CH), 3.36 (2H, d, J = 3.6 Hz, CH_2N), 3.57 (4H, br s, 2 x NH_2), 4.34 (1H, br t, J = 2.4 Hz, CHN), 5.98-6.11 (1H, m, ArH), 6.18 (1H, d, J = 2.7 Hz, ArH), 6.76 (1H, d, J = 8.7 Hz, ArH), 6.96 (1H, d, J = 1.5 Hz, ArH), 7.61-7.70 (2H, m, ArH), 7.95-7.98 (1H, m, ArH), 8.04 (1H, s, ArH), 8.46 (1H, m, ArH); ESMS (*m/z*) 464 ($M+H^+$).

EXAMPLE 111

2-(4-Methoxy-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

NaH (13.8 mg, 0.35 mmol) was added to a solution of the hydroxyl compound 54 (100 mg, 0.27 mmol) in 25 ml of DMF and the mixture stirred for 15 min. Me_2SO_4 (0.030 ml) was added and the stirring continued for an additional

18 h. The mixture was concentrated and the residue was taken up in 75 ml EtOAc. The solution was extracted successively with Na_2CO_3 (2 x 50 ml) and 1N HCl (2 x 50 ml), dried and stripped. Purification by Chromatotron using hexane/EtOAc 4:1 as an eluent gave the compound 111 as a white powder (132 mg, 93.0 %). ^1H NMR ($CDCl_3$): δ 1.45-1.52 (6H, m, alkyl), 1.82-1.96 (6H, m, alkyl), 2.25 (1H, br s, -CH-), 3.50 (2H, q, J = 3.6 Hz, $-CH_2N-$), 4.05 (3H, s, Me), 4.53 (1H, br s, -CHN-), 7.11 (1H, s, ArH), 7.82-7.91 (2H, m, 2 x ArH), 7.89 (1H, d, J = 3.6, ArH), 7.98 (1H, s, ArH), 8.27 (1H, d, J = 4.2 Hz, ArH); Anal. Calcd. for $C_{21}H_{25}NO_3S$; C, 67.80; H, 6.78; N, 3.77; S, 8.63. Found: C, 67.75; H, 6.76; N, 3.70; S, 8.57. ESMS 372 (*m/z*) (M + H^+).

EXAMPLE 112

2-(4-(2-Pyridylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Cs_2CO_3 (0.25 g, 0.75 mmol) was added to a solution of the hydroxyl compound 54 (0.043 g, 0.12 mmol), 2-picolylchloride hydrochloride (0.021 g, 0.13 mmol) and a crystal of KI in DMF (5 ml). The mixture was stirred at 100 °C for 15 hr. At this time the solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The EtOAc phase was washed with brine, dried (Na_2SO_4), stripped and the residue was purified by flash chromatography using 10% EtOAc in $CHCl_3$ to give 50 mg of the compound 112. ^1H NMR ($CDCl_3$): δ 1.15-1.59 (m, 6 H), 1.65-1.98 (m, 6 H), 2.21 (m, 1 H), 3.40 -3.80 (m, 2 H), 4.43 (m, 1 H), 5.46 (s, 2 H), 7.10-7.30 (m, 2 H), 7.51-7.81 (m, 4 H), 7.84-8.05 (m, 2 H), 8.32-8.49 (m, 1 H), 8.55-8.65 (m, 1 H). ESMS *m/z* 449 (MH^+). mp. 152-153 °C

EXAMPLE 113

2-(4-(4-Pyridylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 113 (50 mg) was prepared as above in Example 112 from the hydroxyl compound 54 (0.43 g, 0.12 mmol), 4-picolylchloride hydrochloride (0.21 g, 0.13 mmol) and Cs_2CO_3 (0.25 g, 0.75 mmol) in DMF (5 ml). ^1H NMR ($CDCl_3$): δ 1.15-1.65 (m, 6 H), 1.65-2.15 (m, 6 H), 2.21 (m, 1 H), 3.50 (m, 2 H), 4.23 (m, 1 H), 5.50 (s, 2 H), 7.25 (s, 1 H), 7.51-7.70 (m, 2 H), 7.70-7.90 (m, 2 H), 8.05 -8.20 (m, 2 H), 8.51-8.62 (m, 1 H), 8.65-8.95 (m, 2 H). ESMS *m/z* 449 (MH^+). mp. 138-139 °C.

EXAMPLE 114

2-(4-(2-(1-Methyl-2-pyrrolidinyl)ethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 114 (30 mg) was prepared as in Example 112 from the hydroxyl compound 54 (0.43 g, 0.12 mmol), 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (0.22 g, 0.12 mmol) and Cs_2CO_3 (0.25 g, 0.75 mmol) in DMF (5 ml). ^1H NMR ($CDCl_3$): δ 1.40-1.60 (m, 6 H), 1.62-2.02 (m, 8 H), 2.12-2.32 (m, 3 H), 2.50 (s, 3 H), 2.60-2.87 (m, 4 H), 2.87-3.05 (m, 1 H), 3.50 (s, 2 H), 4.23 (m, 1 H), 4.95 (m, 2 H), 7.12 (s, 1 H), 7.51-7.70 (m, 2 H), 7.70-8.05 (m, 2 H), 8.25 -8.40 (m, 2 H). ESMS *m/z* 469 (MH^+).

EXAMPLE 115

2-(4-(1-Methyl-2-piperidylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 115 (30 mg) was prepared as in Example 112 from the hydroxyl compound 54 (0.43 g, 0.12 mmol), 2-chloromethyl-1-methylpiperidine hydrochloride (0.22 g, 0.12 mmol) and Cs_2CO_3 (0.25 g, 0.75 mmol) in DMF (5 ml). ESMS *m/z* 469 (MH^+)

EXAMPLE 116

2-(4-(6-Methyl-3-pyridylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 116 (190 mg) was prepared as in Example 112 from the hydroxyl Compound 54 (0.15 g, 0.42 mmol), 6-methyl-3-picolyl chloride (0.094 g, 0.53 mmol) and Cs_2CO_3 (0.38 g, 1.16 mmol) in DMF (5 ml). ^{1}H NMR ($CDCl_3$): δ 1.15-1.65 (m, 6 H), 1.65-2.15 (m, 6 H), 2.21 (m, 1 H), 3.50 (m, 2 H), 4.23 (m, 1 H), 5.50 (s, 2 H), 7.25 (s, 1 H), 7.51-7.70 (m, 2 H), 7.70-7.90 (m, 2 H), 8.05 - 8.20 (m, 2 H), 8.51-8.62 (m, 1 H), 8.65-8.95 (m, 2 H). ESMS *m/z* 463 (MH^+)

EXAMPLE 117

5-Chloro-N-(2-oxo-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl)-2-naphthalenesulfonamide

PCC (0.11g, 0.49 mmol) was added to a solution of compound 67 (0.072 g, 0.19 mmol) in 50 ml CH_2Cl_2 containing NaOAc (0.082 g, 0.98 mmol) and the slurry stirred for 4 h. The mixture was concentrated and the residue was dissolved in 75 ml of EtOAc. The EtOAc layer was extracted with 2 x 50 ml 1N HCl and 2 x 50 ml saturated $NaHCO_3$, then filtered through 40 g of silica and concentrated. Purification by Chromatotron using hexane/EtOAc (5:1) as an eluent afforded a solid which was crystallized from hexane/EtOAc to give compound 117 as white crystals (0.63 g, 81.4 %). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, s, Me), 0.89 (3H, s, Me), 0.91 (3H, s, Me), 1.32-1.40 (^{1}H, m, alkyl), 1.60 (1H, t, J = 3.0 Hz, alkyl), 2.00 (1H, m, alkyl), 2.38 (1H, d, J = 1.5 Hz, alkyl), 3.18 (1H, d, J = 1.5 Hz, alkyl), 5.12 (1H, d, J = 3.0 Hz, -N$\underline{H}$CO), 7.51 (1H, t, J = 8.1 Hz, ArH), 7.70 (1H, d, J = 9.0 Hz, ArH), 7.90 (1H, d, J = 10.0 Hz, ArH), 7.95 (1H, dd, J = 7.2, 1.8 Hz, ArH), 8.41 (1H, d, J = 9.0 Hz, ArH), 8.46 (1H, d, J = 1.5 Hz, ArH).

EXAMPLE 118

2-(4-Carboxy-2-naphthalenesulfonyl)-2-azatricylco[4.3.1.1^{4,8}]undecane

Trifluoromethanesulfonic anhydride (0.113 ml, 671 mmol) was added to a solution of compound 54 (200 mg, 560 mmol) in anhydrous CH_2Cl_2 (30 ml) followed by DIEA (0.119 ml, 727 mmol) and the resulting mixture was stirred at room temperature for 1 h. The solution was extracted with 1N HCl (2 x 50 ml), and the organic layer was dried over Na_2SO_4 and then filtered through a silica plug (20 g) and concentrated to give a coloress oil (0.227 mg, 83.0 %).

The above compound (0.227 mg, 464 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2 (20 ml) and MeOH (20 ml). To this solution were added successively $Pd(OAc)_2$ (10 mg, 46.4 mmol), 1,3-bis(diphenylphosphino)propane (DPPP, 19 mg, 46.4 mmol) and DIEA (0.759 ml, 4.64 mmol). CO gas was bubbled through for 5 min until saturation and the solution was stirred under an atmosphere of CO for 72 hr and concentrated. The residue was dissolved in EtOAc (50 ml) and the solution was extracted with 1N HCl (2 x 50 ml) followed by satd. $NaHCO_3$ (2 x 50 ml) and filtered through 20 g of silica. Further purification by Chromatotron using hexane/EtOAc/CH_2Cl_2 (6:1:1) afforded white crystals (0.151 g, 81.4 %). ^1H NMR ($CDCl_3$): δ 1.47-1.51 (6H, m, alkyl), 1.85-1.89 (6H, m, alkyl), 2.28 (1H, br s, alkyl), 3.50 (2H, d, J = 3.6 Hz, -NC$\underline{H_2}$-), 4.03 (3H, s, Me), 4.45 (1H, br s, -NC$\underline{H}$-), 7.56 (1H, t, J = 7.8 Hz, ArH), 7.51-7.83 (2H, m, ArH), 8.52 (2H, d, J = 5.1 Hz, ArH), 8.98 (1H, d, J = 8.4 Hz). ESMS *m/z* 400 (MH^+).

The above methyl ester compound (0.100 g, 0.250 mmol) was dissolved in MeOH (20 ml) and treated with a solution of $LiOH{\cdot}H_20$ (0.011 g, 0.275 mmol) in H_2O (5 ml) and the solution was stirred for 2 h. The mixture was concentrated and the residue was dissolved in 50 ml EtOAc. The solution was extracted with 1N HCl and the organic layer was dried and stripped. The

residue, upon purification by Chromatotron using hexane/EtOAc/MeOH (6:1:0.5) as an eluent, afforded compound 118 as a white solid (0.091 g, 95 %). ESMS *m/z* 385 (MH^+).

EXAMPLE 119

2-(4-(1-Ethyl-2-pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

119a. 2-(4-(1-tert-Butyloxycarbonyl-2-pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 119a (0.18g) was prepared by a method similar to that of Example 111 from the hydroxyl compound (compound 54, 0.258 g, 0.72 mmol), (S)-1-tert-Butyloxycarbonyl-2-pyrrolidinylmethyl bromide (0.23 g, 0.87 mmol; J. Das, et al; J. Med. Chem. 1992, 35, 2610-2617) and Cs_2CO_3 (1.25 g, 3.5 mmol) in DMF (5 mL).

119b. 2-(4-(2-Pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

A solution of the above N-Boc compound 119a in a mixture of CH_2Cl_2 (20 mL) and TFA (15 mL) was stirred for 18 h at room temperature. The solution was evaporated and dried under high vacuum to yield a viscous gum (0.17 g). ESMS *m/z* 441 (MH+).

119c. 2-(4-(1-Acetyl-2-pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Acetic anhydride (68 μL, 0.66 mmol) was added to a solution of the above compound 119b (0.14 g, 0.34 mmol) and pyridine (39 μL, 0.42 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 18 h at room temperature. The solution was evaporated and the residue was taken up in EtOAc (50 mL). The EtOAc solution was washed with water, dried and evaporated. The residue was purified by flash chromatography

(CH_2Cl_2/MeOH (2%) to yield compound 119c as a foam (0.07 g). ESMS *m/z* 483 (MH+)

$LiAlH_4$ (0.2 mL, 1M THF) was added to a solution of the above N-acetyl compound 120c (0.07 g, 0.14 mmol) in THF (7 mL) at 0°C and stirred for 30 min. The ice-bath was removed and the solution was refluxed for 3 h. The solution was cooled in ice and treated with saturated Na_2SO_4 (3 mL). After stirring for 15 min. the solution was filtered and the residue was washed with EtOAC. The filtrate and the washings were combined and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2/MeOH (1%) to yield the title compound 119 as an oil (0.03 g). ESMS *m/z* 469 (MH+)

EXAMPLE 120

2-(4-(1-Methyl-2-pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane

Compound 120 was prepared from 2-(4-(1-tert-Butyloxycarbonyl-2-pyrrolidinylmethyloxy)-2-naphthalenesulfonyl)-2-azatricyclo[4.3.1.1^{4,8}]undecane (0.07 g) via $LiAlH_4$ (0.2 mL) reduction as described in Example 120. ESMS *m/z* 455 (MH+).

EXAMPLE 121

N-(5-Chloro-2-naphthalenesulfonyl)piperidine

Compound 121 was prepared using a procedure similar to the procedure used in Example 1 by replacing cyclohexylamine with piperidine. The pure compound 121 was obtained as a yellow solid by recrystallization of the crude compound from hexane/EtOAc; mp. 162-163°C. ^1H NMR (CDC13): δ 8.40 (δ, J=8.9, 1 H, H3), 8.33 (d, J=1.5, 1 H, H1), 7.90 (d, J=8.3, 1 H, H6), 7.86 (d, J=8.9, 1H,H4) 7.73 (d, J=7.5, 1 H,H8), 7.53 (t,J=7.9, 1H, H7), 3.09-3.04 (m, 4 H, alkyl H's), 1.69-1.62 (m, 4 H, alkyl's), 1.44-1.38 (m, 2 H, alkyl's); anal. calcd. for C15H16NO2SCl;

C, 58.15; H, 5.21; N, 4.52; found: X, 58.22, H, 5.18; N, 4.53.

EXAMPLE 122

N-(5-Chloro-2-naphthalenesulfonyl)thiomorpholine

Compound 122 was prepared using a procedure similar to the procedure used in Example 1 by replacing cyclohexylamine with thiomorpholine. The pure product was obtained as an amber solid by recrystallization the crude compound from hexane/EtOAc; mp.139.6-140.2°C. ^{1}H NMR (CDC13): δ 8.38 (δ, J=9.0, 1 H, H3), 8.32 (d, J=1.8, 1 H, H1), 7.88 (d, J=8.3, 1 H, H6), 7.81 (d, J=8.9, 1H,H4) 7.72 (d, J=7.5, 1 H,H8), 7.52 (t,J=7.9, 1 H, H7), 3.43-3.39 (m, 4 H, alkyl H's), 2.75-2.69-1.62 (m, 4 H, alkyl's).

EXAMPLE 123

N-(5-Iodo-2naphthalenesulfonyl)homopiperazin

Compound 123 was prepared using a procedure similar to the procedure used in Example 1 by replacing cyclohexylamine with homopiperazine.

REFERENCE EXAMPLE

4-Acetoxy-2-naphthalenesulfonyl chloride

1-Hydroxynaphthalene-3-sulfonic acid sodium salt (TCI Chemical Co.) (10.0 g, 40.6 mmol) was suspended in DMF (100 ml) to provide a thick black mixture. Pyridine (12 g) and acetic anhydride (5 g, 48.7 mmol) were added and the mixture was stirred at room temperature for 18 h. At this time the solvent was evaporated and the black residue was dissolved in $CHCl_3$ (200 ml). Phosphorusoxytrichloride (9.4 ml, 101.5 mmoL) was added and the mixture was stirred at room temperature for 18 h. At this time the reaction mixture was quenched by addition of 2N HCL (100 ml). The $CHCl_3$ phase was collected, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography ($CHCl_3$) to provide the pure sulfonyl chloride as a yellow solid. This was dissolved in hot

$CHCl_3$/hexane (5/1) and the product crystallized to give pink crystals (8.58 g, 74%): ^1H NMR ($CDCl_3$): δ 2.51 (s, 3, $COCH_3$), 7.69-7.87 m (3H, m, 3 x ArH), 7.96-8.08 (m, 2H, 2 x ArH), 8.47-8.54 (m, 1H, ArH).

Part IV: Pharmacology and Biological Assays

In order to establish the pharmacological properties of the compounds of Formula (I) as a method of treatment for immuno-inflammatory disease in a patient suffering therefrom -- such diseases being for the most part, but not limited exclusively to, graft rejection, ischemia reperfusion, asthma/allergy, delayed type hypersensitivity and AIDS -- an *in vitro* assay was used to determine the effect of the compounds of the present invention on β_2 mediated adhesion. Because human endothelial cells (ECs) express low levels of ICAM-1 on their surface and stimulation with TNF-α increases its expression, adhesion of lymphocytes can be measured following the principal assay design as described below for the human B cell line JY.

A. Cell Adhesion to Stimulated Endothelial Cells

Human umbilical vein endothelial cells (HUVEC) are purchased from Clonetics (San Diego, CA) at passage number 2. The cells are grown in flasks pre-coated with 0.5% porcine skin gelatin (Sigma, St. Louis, MO) in EGM-UV media (Clonetics, San Diego, CA) supplemented with 10% fetal bovine serum. Cells are re-fed every 2-3 days, reaching confluence by day 4 to 6. The cells are monitored for Factor VIII antigen and our results show that at passage 12, the cells are positive for this antigen. The endothelial cells are not used following passage 7. Endothelial cells are grown to confluency in 96-well micro-titer assay plate.

The human B cell line JY was cultured in RPMI media containing 10% fetal calf serum at 37°C in a

humidified CO_2 atmosphere. JY cells are loaded with the fluorescent dye indicator BCECF as follows: JY cells are washed twice with HBSS and cells are then re-suspended in HBSS at 5 x 10^6 cells/ml; BCECF-AM (Molecular Probes), stock concentration = 1 mg/ml in DMSO, is added to the JY cells to a final concentration of 2 μg/ml; cells are incubated in the dark at 37°C for 30-45 minutes; washed twice with HBSS and used in the assay.

The compounds presented in this invention are typically dissolved in 2.5 mg HSA/ml DME at four times the assay concentration and pH adjusted with 7.5% sodium bicarbonate as needed. A confluent monolayer of human ECs in microtiter plates is stimulated with 50 U/ml TNF-α for 20 hours, and on the next day is washed twice with DMEM-HSA before use. The ECs may be fixed by treatment with 3% paraformaldehyde. The assay plate is placed on ice, and test compound is added to quadruplicate wells, then all wells received 2.5 x 10^5 labeled JY cells and an optional stimulus (e.g. phorbol ester). The plates are incubated for 30 minutes at 37°C in a CO_2 incubator. The plates are washed four times with 100 μl PBS/well and the fluorescence of the adherent cells is measured using a fluorescence reader. Fluorescence in each well is measured as Arbitrary Fluorescence Units and percent adhesion in the absence of the test compound is adjusted to 100% and the percent adhesion in the presence of the text compound is calculated.

Inhibitory concentrations (IC_{50}) are determined based on 100% adhesion of cells that were incubated in the absence of drugs. Stimulation of protein kinase C by phorbol esters such as 13,14-phorbol myristate acetate (PMA) increases the observed adhesion approximately 5-fold. This PMA induced adhesion is 100% blocked by anti-LFA-1 or anti-CD18 antibodies and about 75-80% blocked by anti-ICAM-1 antibodies, while it is unaffected by antibodies to Mac-1, α_4 or control

antibodies. Thus, this assay measures preferentially the interaction between ICAM-1 and LFA-1.

The effect of the compounds of the present invention on cell adhesion mediated by β_2 integrin can also be measured using purified recombinant ICAM-1 as an adhesion substrate. Adhesion of BCECF-AM-labelled JY cells to 96-well assay plates pre-coated with ICAM-1 is performed as described for adhesion to endothelial cells. Assay plates are coated with purified ICAM-1 for 24 hours at $4^{o}C$ and washed three times with HBSS before use.

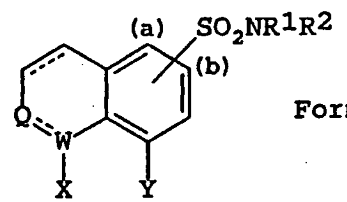
B. <u>Evaluation of Cytotoxicity *In Vitro*</u>

Cytotoxicity of the most active compounds was evaluated *in vitro* by measuring uptake of propidium iodide or in an ALAMAR BLUE assay according to the manufacturer's specifications (Alamar Biosciences, Inc., 4110 N. Freeway Blvd., Sacramento, California 95834). The activity in the assay JY EC_{50} assay was not due to cytotoxic activity of the compounds. The compounds of Examples 3 and 5 did not inhibit the proliferation, measured at 20 hours, of JY cells or U937 cells at concentrations at which they were active in the adhesion assay.

Part V

TABLE 1

Selected Sulfonamides

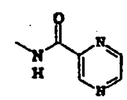


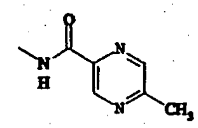
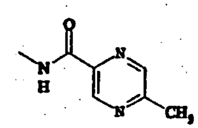
Formula (I)

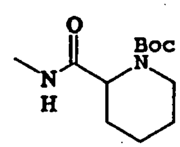
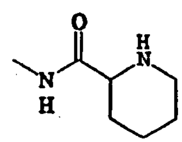
Unless otherwise noted, the both dashed bonds are unsaturated.

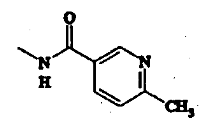
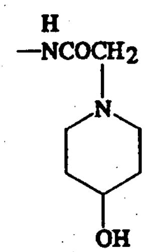
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
3	C	C	Cl	H	(b)	str. 3
5	C	C	Cl	H	(b)	str. 4
15	C	C	Cl	H	(b)	str. 9

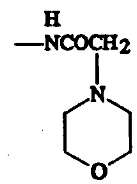
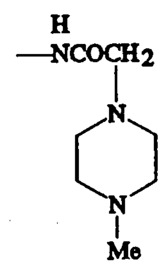
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
16	C	C	Cl	H	(b)	str. 1
18	C	C	Cl	H	(b)	str. 2
19	C	C	Cl	H	(b)	str. 7
22	C	C	Cl	H	(b)	str. 8
27	C	N	H	H	(b)	str. 4
28	C	N	H	H	(b)	str. 3
29	C	N	H	H	(b)	str. 1
32	C	C	$-NH_2$	H	(b)	str. 4
34@	C	N	H	H	(b)	str. 3
39	C	C	H	-OMe	(a)	str. 4
50	C	C	$-OCOCH_3$	H	(b)	str. 3
51	C	C	H	$-OCOCH_3$	(b)	str. 4
52	C	C	H	OH	(b)	str. 4
56	C	C	H	$-OCH_2$-Py(3)	(b)	str. 4
61	C	C	H	$-OCH_2$-Py(3)	(b)	str. 1
64-1	C	C	-NHCbz	H	(b)	str. 1
64-2	C	C	$-NH_2$	H	(b)	str. 1
65-1	C	C	-NHCbz	H	(b)	str. 2

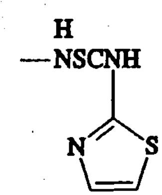
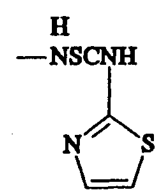
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
65-2	C	C	$-NH_2$	H	(b)	str. 2
66-1	C	C	-NHCbz	H	(b)	str. 3
66-2	C	C	$-NH_2$	H	(b)	str. 3
67	C	C	Cl	H	(b)	str. 5
68	C	C	$-NHCO-CH_2Py(3)$	H	(b)	str. 1
69	C	C		H	(b)	str. 1

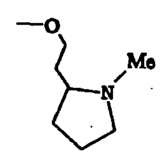
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
70	C	C		H	(b)	str. 1
71	C	C		H	(b)	str. 3
72	C	C	-NHCO-Py(2)	H	(b)	str. 1
73	C	C	-NHCO-Furan(2)	H	(b)	str. 1
74	C	C	-NHCOPh-NO_2(2)	H	(b)	str. 1
75	C	C	-NHCOPh-NH_2(2)	H	(b)	str. 1

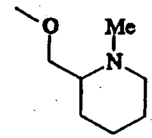
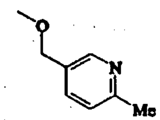
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
76	C	C	$-NHCOPh-NO_2(3)$	H	(b)	str. 1
77	C	C	$-NHCOCH_3$	H	(b)	str. 1
78	C	C	$-NHCO-(CH_2)_3NHBoc$	H	(b)	str. 1
79	C	C	$-NHCO-(CH_2)_3NH_2$	H	(b)	str.1
80	C	C		H	(b)	str. 1
81	C	C		H	(b)	str. 1
82	C	C	$-NHCOCH_2NHBoc$	H	(b)	str. 2

Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
83	C	C	$-NHCOCH_2NH_2$	H	(b)	str. 2
84	C	C	$-NHCOPh-CO_2Me(4)$	H	(b)	str. 1
85	C	C	$-NHCOPh-CO_2H(4)$	H	(b)	str. 1
86	C	C		H	(b)	str. 1
91	C	C	$-NHCOCH_2NMe_2$	H	(b)	str. 2
92	C	C		H	(b)	str. 2

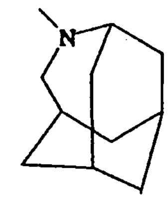
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
93	C	C		H	(b)	str. 2
94	C	C		H	(b)	str. 2
95	C	C	$-NHCOCH_2NMe_2$	H	(b)	str. 3
96	C	C	-NHCSNH-COPh	H	(b)	str. 2
97	C	C	-NHCSNH-COPh	H	(b)	str. 3
98	C	C	$-NHCSNH_2$	H	(b)	str. 2

Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
99	C	C		H	(b)	str. 2
100	C	C		H	(b)	str. 1
101	C	C	$-NHCH_2-Py(3)$	H	(b)	str. 1
102	C	C	-NHPh-2,4-dinitro	H	(b)	str. 1
103	C	C	H	-OPh-2,4-dinitro	(b)	str. 1
104	C	C	H	-OPh-4-nitro	(b)	str. 1
105	C	C	OPh-4-nitro	H	(b)	str. 4

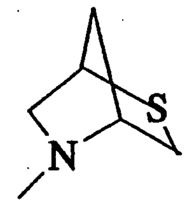
Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
106	C	C	H	-OPh-2-nitro-4-Me	(b)	str. 1
107	C	C	H	-OPh-2-nitro-5-Me	(b)	str. 1
108	C	C	H	-OPh-2-nitro-4-CF_3	(b)	str. 1
109	C	C	H	-OPh-4-amino	(b)	str. 1
110	C	C	H	-OPh-2,4-diamino	(b)	str. 1
111	C	C	H	-OMe	(b)	str. 1
112	C	C	H	$-OCH_2Py(2)$	(b)	str. 1
113	C	C	H	$-OCH_2Py(4)$	(b)	str. 1
114	C	C	H		(b)	str. 1

Cmpd NO.	Q	W	X	Y	$-SO_2-$ RING POSITION	$-NR^1R^2$
115	C	C	H		(b)	str. 1
116	C	C	H		(b)	str. 1
117	C	C	Cl	H	(b)	str. 6

@1,2,3,4-tetrahydroquinoline; both dashed bonds are saturated.



Str. 1



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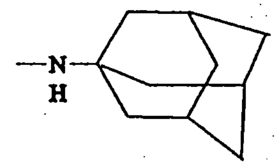
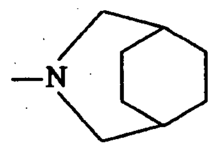


Str. 3



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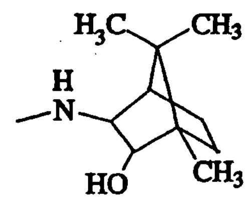

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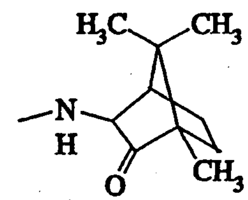

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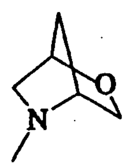

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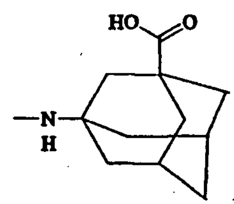

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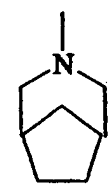


Str. 9

Part VI: Pharmaceutical Compositions

As indicated previously, the inventive compounds of formula I can be formulated into pharmaceutical compositions. In determining when a compound of formula I is indicated for the treatment of a given disease, the particular disease in question, its severity, as well as the age, sex, weight, and condition of the subject to be treated, must be taken into consideration and this perusal is to be determined by the skill of the attendant physician.

For medical use, the amount of a compound of Formula I required to achieve a therapeutic effect will, of course, vary both with the particular compound, the route of administration, the patient under treatment, and the particular disorder or disease being treated. A suitable dose of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for a mammalian subject suffering from, or likely to suffer from, any condition as described hereinbefore is 0.1 μg to 500 mg of the compound of formula I, per kilogram body weight of the mammalian subject. In the case of systematic administration, the dose may be in the range of 0.5 to 500 mg of the compound per kilogram body weight, the most preferred dosage being 0.5 to 50 mg/kg of mammal body weight administered two to three times daily. In the case of topical administration, e.g., to the skin or eye, a suitable dose may be in the range of 0.1 μg to 100 μg of the compound per kilogram, typically about 0.1 μg/kg.

In the case of oral dosing, a suitable dose of a compound of Formula I, or a physiologically acceptable salt thereof, may be as specified in the preceding paragraph, but most preferably is from 1 mg to 10 mg of the compound per kilogram, the most preferred dosage being from 1 mg to 5 mg/kg of mammal body weight, for example, from 1 to 2 mg/kg. Most

preferably, a unit dosage of an orally administrable composition encompassed by the present invention contains less than about 1.0 g of a formula I compound.

It is understood that the ordinarily skilled physician or veterinarian will readily determine and prescribe the effective amount of a compound of Formula I to prevent or arrest the progress of the condition for which treatment is administered. In so proceeding, the physician or veterinarian could employ relatively low doses at first, subsequently increasing the dose until a maximum response is obtained.

The compounds and compositions of the present invention can be administered to patients suffering from a condition listed herein in an amount which is effective to fully or partially alleviate undesired symptoms of the condition. The symptoms may be caused by inappropriate cell adhesion mediated β_2 integrins. Such inappropriate cell adhesion would typically be expected to occur as a result of increased ICAM-1 expression on the surface of endothelial cells. Increased ICAM-1 expression can be due to a normal inflammation response or due to abnormal inflammatory states. In either case, an effective dose of a compound of the invention may reduce the increased cell adhesion due to increased ICAM-1 expression by endothelial cells. Reducing the adhesion observed in the disease state by 50% can be considered an effective reduction in adhesion. More preferably, a reduction in adhesion by 90%, is achieved. Most preferably adhesion mediated by ICAM-1/LFA-1 interaction is abolished by an effective dose. Clinically, in some instances, effect of the compound can be observed or a decrease in white cell infiltration into tissues or a site of injury. To achieve a therapeutic effect, then, the compounds or compositions of the present invention are administered

to provide a dose effective to reduce or eliminate inappropriate cell adhesion or to alleviate undesired symptoms.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising a compound of Formula I and a pharmaceutically acceptable carrier therefor. Such formulations constitute a further feature of the present invention.

The formulations, both for human and veterinary medical use, of the present invention comprise an active ingredient of Formula I, in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s), which are generally known to be effective in treating the disease or condition encountered. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), intra-articular, topical, nasal inhalation (e.g., with an aerosol) or buccal administration. Such formulation are understood to include long-acting formulations known in the art.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods may include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired form.

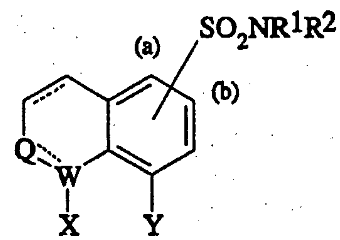
Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient in the form of a powder or granules; in the form of a solution or suspension in an aqueous liquid. Formulations for other uses could involve a nonaqueous liquid; in the form of an oil-in-water emulsion or a water-in-oil emulsion; in the form of an aerosol; or in the form of a cream or ointment or impregnated into a transdermal patch for use in administering the active ingredient transdermally, to a patient in need thereof. The active ingredient of the present inventive compositions may also be administered to a patient in need thereof in the form of a bolus, electuary, or paste.

The practitioner is referred to "Remington: The Science and Practice of Pharmacy," 19th Edition, c. 1995 by the Philadelphia College of Pharmacy and Science, as a comprehensive tome on pharmaceutical preparations.

CLAIMS

What is claimed is:

1. A compound of the Formula (I):



(I)

wherein:

W and Q are selected from a carbon and a nitrogen atom, provided that W and Q are not both simultaneously nitrogen atoms;

wherein (a) and (b) denote the ring positions which can be substituted with the sulfonamide group;

wherein dashed bonds indicate optionally saturated or unsaturated bonds;

wherein X and Y can be the same or different and are selected from a hydrogen atom, a halogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, -CN, $-NO_2$, $-SO_2NH_2$, $-COOR^3$, $-(CH_2)_mOR^3$, $-CONHR^4$, $-NHCO(CH_2)_nR^5$, $-NH(CS)NH(CO)_pR^6$, $-NH(CO)NHR^7$, or $-(CO)_qNR^8R^9$, wherein m is an integer of 0 to 3, n is an integer of 0 to 3, p is 0 or 1 and q is 0 or 1;

wherein R^1 and R^2 are the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, amine-substituted C_{1-8} alkyl, C_{3-9} cycloalkyl, aryl, 1-adamantyl, 2-adamantyl, 1-adamantanemethyl, 3-noradamantyl, 3-quinuclidinyl, 3-carboxy-1-adamantyl, 2-oxaadmant-1-yl, 1-azaadamant-4-yl, 3-hydroxy-1-adamantyl, 1-hydroxy-2-azahomoadamant-6-yl, 1-hydroxy-4-azahomoadamant-4-yl, 2-oxa-1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, and 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form either (i) a substituted or unsubstituted monocyclic moiety containing from 5 to 15 ring atoms, or (ii) a substituted or unsubstituted bridged polycyclic moiety containing from 6-20 ring atoms;

wherein R^3 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, carboxy-substituted C_{1-8} alkyl, C_{1-8} alkyl substituted by a substituted or unsubstituted aliphatic heterocyclic group, aryl, heteroaryl, substituted aryl, substituted heteroaryl, substituted or unsubstituted aryl-substituted C_{1-8} alkyl, substituted or unsubstituted heteroaryl-substituted C_{1-8} alkyl, C_{2-8} alkanoyl, amine-substituted C_{1-8} alkyl and $-(CH_2)_r(CO)_sR^{10}$, wherein R^{10} is a hydrogen atom, -OH, C_{1-8} alkyl, C_{1-8} alkyloxy, amine-substituted C_{1-8} alkyl or a substituted or unsubstituted 5- or 6-membered saturated or unsaturated heterocyclic group containing at least one nitrogen atom; r is an integer ranging from 1 to 3 and s is 0 or 1;

wherein R^4 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally

be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{11}$, wherein R^{11} is hydrogen or C_{1-8} alkyl, and $-NR^{12}R^{13}$, wherein R^{12} and R^{13} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl;

R^5 is selected from the group consisting of a hydrogen atom, a halogen atom, C_{1-8} alkyl, C_{1-8} alkyloxycarbonylamino, $-NH_2$, di-C_{1-8} alkylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxy, aryl-substituted C_{1-8} alkyloxy, heteroaryl-substituted C_{1-8} alkyloxy, amine-substituted C_{1-8} alkyl, and a substituted or unsubstituted 5- or 6-membered saturated or unsaturated heterocyclic group containing at least one nitrogen atom and optionally, one oxygen atom or one sulfur atom;

R^6 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{14}$, wherein R^{14} is a hydrogen atom or C_{1-8} alkyl, and $-NR^{15}R^{16}$, wherein R^{15} and R^{16} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl;

R^7 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl and heteroaryl-substituted C_{1-8} alkyl; wherein said aryl or heteroaryl groups may optionally be substituted with one, two or three substituents

selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{17}$, wherein R^{17} is hydrogen atom or C_{1-8} alkyl, and $-NR^{18}R^{19}$, wherein R^{18} and R^{19} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyloxycarbonyl;

R^8 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl, C_{1-8} alkyloxycarbonyl and a benzyloxycarbonyl group; wherein said aryl, heteroaryl or benzyloxycarbonyl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, $-CO_2R^{20}$, wherein R^{20} is hydrogen atom or C_{1-8} alkyl;

R^9 is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, hydroxy-substituted C_{1-8} alkyl, aryl-substituted C_{1-8} alkyl, heteroaryl-substituted C_{1-8} alkyl, C_{1-8} alkyloxycarbonyl and a benzyloxycarbonyl group; wherein said aryl, heteroaryl or benzyloxycarbonyl groups may optionally be substituted with one, two or three substituents selected from the group consisting of a C_{1-8} alkyl group, a halogen atom, $-CF_3$, -CN, -OH, $-NO_2$, a C_{1-8} alkyloxy group, a C_{1-4} carboxylic acid and $-CO_2R^{21}$, wherein R^{21} is hydrogen or C_{1-8} alkyl;

or $-NR^8R^9$ can form a saturated heterocyclic group containing 5 or 6 ring atoms;

or a pharmaceutically acceptable salt thereof;

provided that 3-(2-naphthylsulfonyl)-3-azabicyclo[3.2.2]nonane and a salt thereof are excluded from Formula (I).

2. A compound of claim 1, wherein in R^3, the substitutions of said substituted aryl group, substituted aliphatic heterocylic group or substituted heteroaryl group number from 1 to 3 and are selected from a C_{1-3} alkyl group, a C_{1-3} alkyloxy group, a halogen-substituted C_{1-3} alkyl group, a C_{1-4} alkloxycarbonyl group, $-NO_2$, -OH and $-NH_2$.

3. A compound of claim 1, wherein in all of R^3 through R^{15}, said aryl groups are phenyl or fluorenyl, and said heteroaryl groups are selected from the group consisting of furyl, pyridyl, pyrazinyl, and thiazolyl, and said aliphatic heterocyclic groups are selected from the group consisting of piperidyl, morpholinyl, piperazinyl and pyrrolidinyl.

4. A compound of claim 1, wherein R^1 and R^2, together with the nitrogen atom to which they are both attached, form a moiety selected from the group consisting of piperidyl, 3-azabicyclo[3.3.2]dec-3-yl, 3-azabicyclo[3.2.2]non-3-yl, 3-azabicyclo[3.2.1]oct-3-yl, 4-azahomoadamant-4-yl, 2-azaadamant-2-yl, 2-thia-5-azabicyclo[2.2.1]hept-5-yl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 5-C_{1-8} alkyloxycarbonyl-2,5-diazabicyclo[2.2.1]hept-2-yl, 5-benzyloxycarbonyl-2,5-diazabicyclo[2.2.1]hept-2-yl and 3-hydroxy-4-azahomoadamant-4-yl.

5. A compound of claim 1, wherein Q and W are each carbon atoms, X is a chlorine atom, Y is a hydrogen atom, R^1 is an adamantyl group and R^2 is a hydrogen atom.

6. A compound of claim 1, wherein Q and W are each carbon atoms, X is a chlorine atom, Y is a

hydrogen atom, and R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl, 2-thia-5-azabicyclo[2.2.1]hept-5-yl or 3-azabicyclo[3.2.2]non-3-yl.

7. A compound of claim 1, wherein Q and W are each carbon atoms, X is $-NH_2$, Y is a hydrogen atom and R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl.

8. A compound of claim 1, wherein Q and W are each carbon atoms, X is $-NHCOR^4$ and Y is a hydrogen atom; wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl; and R^4 is a heteroaryl group.

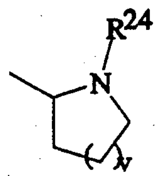
9. A compound of claim 1, wherein Q and W are each carbon atoms, X is $-NHCOR^4$ and Y is a hydrogen atom; wherein R^1 and R^2, together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl, and R^4 is a substituted pyridyl, substituted pyridyl N-oxide or a substituted pyrazinyl.

10. A compound of claim 1, wherein Q and W are each carbon atoms, X is a hydrogen atom and Y is $-OR^3$; wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form either 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl; R^3 is mono-, di- or tri-substituted phenyl, wherein at least one substituent of said phenyl group is $-NO_2$.

11. A compound of claim 1, wherein Q and W are each carbon atoms, X is a hydrogen atom and Y is OR^3; wherein R^1 and R^2 together with the nitrogen atom to

which they are both attached form 4-azahomoadamant-4-yl or 3-azabicyclo[3.2.2]non-3-yl and R^3 is pyridyl methyl or pyridyl N-oxide methyl.

12. A compound of claim 1, wherein Q and W are each carbon atoms, X is a hydrogen atom, Y is OR^3, wherein R^1 and R^2 together with the nitrogen atom to which they are both attached form 4-azahomoadamant-4-yl, R^3 is $-(CH_2)_r(CO)_sR^{10}$, r = 1 to 3, s = 0, R^{10} is an aminoalkyl group having the structure,



wherein v = 1 or 2;

and R^{24} is selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, C_{2-8} alkanoyl, C_{1-8} alkyloxycarbonyl and benzyoyloxycarbonyl.

13. A compound of claim 1, wherein in R^4 the amine of said amine-substituted C_{1-8} alkyl is $-NR^{25}R^{26}$, wherein R^{25} and R^{26} can be the same or different and are selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and aryl-substituted C_{1-8} alkyloxycarbonyl.

14. A compound of claim 1, wherein in R^1 or R^2, the amine of said amine-substituted C_{1-8} alkyl is $-NR^{27}R^{28}$, wherein R^{27} and R^{28} can be the same or different and are selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and arylalkyloxycarbonyl.

15. A compound of claim 1, wherein X or Y is $-NH(CO)(CH_2)_nR^5$ and R^5 is a substituted or unsubstituted 5- or 6- membered saturated or unsaturated heterocyclic group containing at least one ring nitrogen atom, and optionally, one ring oxygen atom or one ring sulfur atom, and wherein said saturated heterocyclic group is attached either by said ring nitrogen atom or by a carbon atom.

16. A compound of claim 15, wherein R^5 is a substituted, saturated heterocyclic group containing 5 or 6 ring atoms and at least one ring nitrogen, wherein said substitution is at a ring nitrogen and is selected from the group consisting of a hydrogen atom, a hydroxy group, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-9} cycloalkyl, C_{2-8} alkanoyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-8} alkyloxycarbonyl and arylalkyloxycarbonyl.

17. A compound of claim 1, wherein X or Y is $-NHCO(CH_2)_nR^5$, and R^5 is a saturated heterocyclic group containing a first heteroatom that is nitrogen and a second heteroatom that is nitrogen, oxygen or sulfur.

18. A compound of claim 1, wherein X or Y is $-(CH_2)_mOR^3$ and R^3 is $-(CH_2)_r(CO)_sR^{10}$, wherein R^{10} is a heterocyclic group containing 5 or 6 ring atoms and containing a first ring heteroatom that is nitrogen and a second ring heteroatom that is nitrogen, oxygen or sulfur.

19. A compound of claim 1, wherein NR^1R^2 together form a substituted or unsubstituted bridged polycyclic moiety having 6 to 20 ring atoms, wherein there are no ring heteroatoms in addition to the nitrogen of NR^1R^2.

20. A compound of claim 1, wherein NR^1R^2 together form a substituted or unsubstituted bridged polycyclic moiety having 7 to 20 ring atoms, wherein there is a second ring heteroatom in addition to the nitrogen of $-NR^1R^2$, wherein said second ring heteroatom is nitrogen, oxygen or sulfur.

21. A compound of claim 1, wherein one of X or Y is a hydrogen atom.

22. A compound of claim 1, wherein one of R^1 or R^2 is hydrogen.

23. A compound of claim 1, wherein R^1 and R^2 together form a substituted monocylic moiety containing from 5-15 ring atoms or a substituted polycyclic moiety containing from 7 to 20 ring atoms; wherein one, two or three of said substitutions are present and are independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2Ph$, -OH, $-CO_2R^{29}$ and $-CONHR^{29}$, wherein R^{29} is a hydrogen atom or C_{1-8} alkyl.

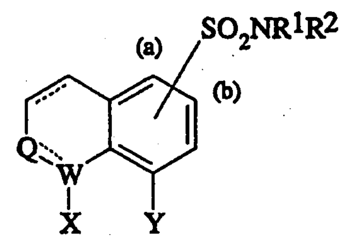
24. A compound of claim 1, wherein in X and/or Y is $-(CO)_qNR^8R^9$, and R^8 and R^9, together with the nitrogen to which they are both attached, form a substituted or unsubstituted saturated heterocyclic group having 5- or 6 ring atoms.

25. A compound of claim 24, wherein said saturated heterocyclic group contains a second heteroatom that is either sulfur or oxygen.

26. A compound of claim 1, wherein the sulfonamide group is attached to the ring at position (b).

27. A compound of claim 1, wherein R^{10} is an amine-substituted C_{1-8} alkyl and said amine is $-NR^{30}R^{31}$, wherein R^{30} and R^{31} can be the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, alkyloxycarbonyl and aryloxycarbonyl.

28. A compound of the Formula (I):



(I)

wherein:

W and Q are selected from a carbon and a nitrogen atom, provided that W and Q are not both simultaneously nitrogen atoms;

wherein (a) and (b) denote the attachment point of the sulfonamide group;

wherein dashed bonds indicate optionally saturated or unsaturated bonds;

wherein X and Y can be the same or different and are selected from a hydrogen atom, a halogen atom, and a polar heteroaryl group;

wherein R^1 and R^2 are the same or different and are selected from the group consisting of a hydrogen atom, C_{1-8} alkyl, amine-substituted C_{1-8} alkyl, C_{3-9} cycloalkyl, aryl, 1-adamantyl, 2-adamantyl, 1-adamantanemethyl, 3-noradamantyl, 3-quinuclidinyl, 3-carboxy-1-adamantyl, 2-oxaadmant-1-yl, 1-azaadamant-4-yl, 3-hydroxy-1-adamantyl, 1-hydroxy-2-azahomoadamant-6-yl, 1-hydroxy-4-azahomoadamant-4-yl, 2-oxa-1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, and 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl;

6-yl, 1-hydroxy-4-azahomoadamant-4-yl, 2-oxa-1-adamantyl, 2-oxa-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl, and 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form either (i) a substituted or unsubstituted monocyclic moiety containing from 5 to 15 ring atoms, or (ii) a substituted or unsubstituted bridged polycyclic moiety containing from 7-20 ring atoms.

29. A compound of claim 1, wherein Q is a carbon atom, W is a carbon atom or a nitrogen atom, and

X is a hydrogen atom, a halogen atom, hydroxy, $-NH_2$, C_{2-8} alkanoyloxy, $-NHCO(CH_2)_nR^5$, $-NH(CS)NH(CO)_pR^6$ or $-(CO)_qNR^8R^9$;

wherein n = 0 or 3 and R^5 is C_{1-8} alkyl, $-NH_2$, aminophenyl, furyl, pyrazinyl, C_{1-8} alkylpyrazinyl, C_{1-8} pyridyl alkyl or piperidyl;

wherein p = 1 and R^6 is phenyl;

wherein R^8 is a hydrogen atom; and

wherein R^9 is dinitrophenyl-C_{1-8} alkyl;

Y is a hydrogen atom, a halogen atom, hydroxy, C_{1-8} alkyl or $-(CH_2)_mOR^3$;

wherein m = 0 and R^3 is carboxy C_{1-8} alkyl, C_{1-8} alkyl, C_{1-8} alkylpyridyl and C_{1-8} alkyl-pyrrolidinyl-C_{1-8} alkyl or phenyl, wherein said phenyl group is optionally substituted by one or two substituents selected from the group consisting of C_{1-8} alkyl, $-NO_2$, $-NH_2$, $-CF_3$, ; and

$-NR^1R^2$ is 1-adamantylamino, (2-oxa-1,7,7-trimethyl-bicyclo[2.2.1]hept-3-yl)amino, 3-azabicyclo[3.2.2]non-3-yl, 3-azabicyclo[3.2.1]oct-3-yl, 4-azahomoadamant-4-yl or 5-aza-2-thiabicyclo[2.2.1]hept-5-yl.

Y is a hydrogen atom or $-(CH_2)_mOR^3$, m = 0, wherein R^3 is methyl or, phenyl substituted with one or two substituents selected from methyl, $-NO_2$, $-CF_3$ or pyridylmethyl; and

$-NR^1R^2$ is 3-azabicyclo[3.2.2]non-3-yl or 4-azahomoadamant-4-yl.

31. A pharmaceutical composition comprising:

at least one compound of any one of claims 1-30, or a pharamaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier, diluent or excipient.

32. Use of a compound of any one of claims 1-30 to make a pharmaceutical composition.

33. The use of claim 32, wherein said pharmaceutical composition is for the prevention or treatment of specific inflammation, non-specific inflammation, ischemia reperfusion injury, asthma, allergy, delayed type hypersensitivity, contact hypersensitivity, rheumatoid arthritis, rhinovirus infections and lymphotrohpic virus infections, or transplant rejection.

34. A method for preventing or treating a disease having an etiology related to abnormal function of a β_2 integrin comprising administering to a patient in need thereof an amount of a pharmaceutical composition of claim 31 effective for restoring normal function of said β_2 integrin.

35. A method for treating or preventing a disease, selected from the group consisting of specific inflammation, non-specific inflammation, ischemia reperfusion injury, asthma, allergy, delayed

type hypersensitivity, contact hypersensitivity, rheumatoid arthritis, rhinovirus infections and lymphotrohpic virus infections, or transplant rejection comprising administering to a patient in need thereof an amount of a compound of claim 1 effective for preventing or treating said specific inflammation, non-specific inflammation, ischemia reperfusion injury, asthma, allergy, delayed type hypersensitivity, contact hypersensitivity, rheumatoid arthritis, rhinovirus infections and lymphotrohpic virus infections, or transplant rejection which comprises administering an effective amount of the compound of claim 1 or 28 to a patient.

36. A pharmaceutical composition comprising:

the compound 3-(2-naphthylsulfonyl)-3-azabicyclo[3.2.2]nonane or a pharamaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier, diluent or excipient.

37. Use of 3-(2-naphthylsulfonyl)-3-azabicyclo[3.2.2]nonane or a pharamaceutically acceptable salt thereof to make a pharmaceutical composition.

38. A method for preventing or treating a disease having an etiology related to abnormal function of a β_2 integrin comprising administering to a patient in need thereof an amount of a pharmaceutical composition of claim 36 effective for restoring normal function of said β_2 integrin.

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 96/10100

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D223/12 A61K31/33 A61K31/18 C07D487/08 C07D495/08
C07D491/08 C07D221/24 C07D295/22 C07C311/47 C07C311/28
C07C311/36 C07C311/16 C07C311/18 C07C311/21 C07C311/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 471 841 (ASAHI KASEI KOGYO KABUSHIKI) 26 February 1992 * example 26,27,30,31,38,39,46,50,51,54-59 * see page 35-36 ---	1,31-33
A	WO,A,92 08464 (TANABE SEIYAKU CO. LTD.) 29 May 1992 see claims -----	31-33

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1996	03.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Intern   nal Application No
PCT/US 96/10100

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   C07D311/00   C07D401/12   C07D471/08   C07D215/36   C07D207/16
C07D241/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
	0 3. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT	International application No. rCT/US 96/ 10100

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

   Claims searched incompletely: 1-3
   Claims not searched: 34, 35, 38

   see attached sheet

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requrements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The vast number of theoretically conceivable compounds comprised under formula (I) of claim 1 precludes a comprehensive documentary search as well as a comprehensive on line search in a structure data base and would not be economically justified (cf. Arts. 6,15 and Rule 33 PCT; see Guidelines B III 2.1).
In accordance with the examples of the present application, the latter search was limited to compounds of formula (I) as an aromatic bicyclic ringsystem with the sulfonamide function in position (b) and wherein -NR1R2 is defined as on page 8-14 of the descriptive part of the present application.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/10100

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-471841	26-02-92	WO-A-	9113875	19-09-91
		CA-A-	2020027	09-09-91
		DE-D-	69023335	07-12-95
		DE-T-	69023335	11-07-96
		NO-B-	177532	26-06-95
		US-A-	5340811	23-08-94
WO-A-9208464	29-05-92	NONE		